NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]

Committee papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]

Contents:

- Dr Martin Duddy – clinical expert, nominated by the Association of British Neurologists
- Ms Sarah Bittlestone – patient expert, nominated by the MS Trust
- Mrs Denise Murray – patient expert, nominated by the MS Trust

10. **Assessment Group specification for the March 2017 Addendum**

11. **Addendum prepared by the Assessment Group in March 2017** as issued to consultees and commentators
    - Addendum
    - Appendix

12. **Consultee and commentator comments on the March 2017 Addendum** from:
    - Bayer
    - Biogen
    - Merck
    - Novartis
    - Teva
    - Multiple Sclerosis Trust
    - Association of British Neurologists
    - Department of Health
    - Sanofi

13. **AG response to the comments on the March 2017 Addendum**

14. **Additional information submitted by the companies in September 2017** from:
    - Biogen
    - Merck
    - Teva

15. **Assessment Group Addendum** prepared by Warwick Evidence in November 2017

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

Committee slides – part 1 (ACIC information)

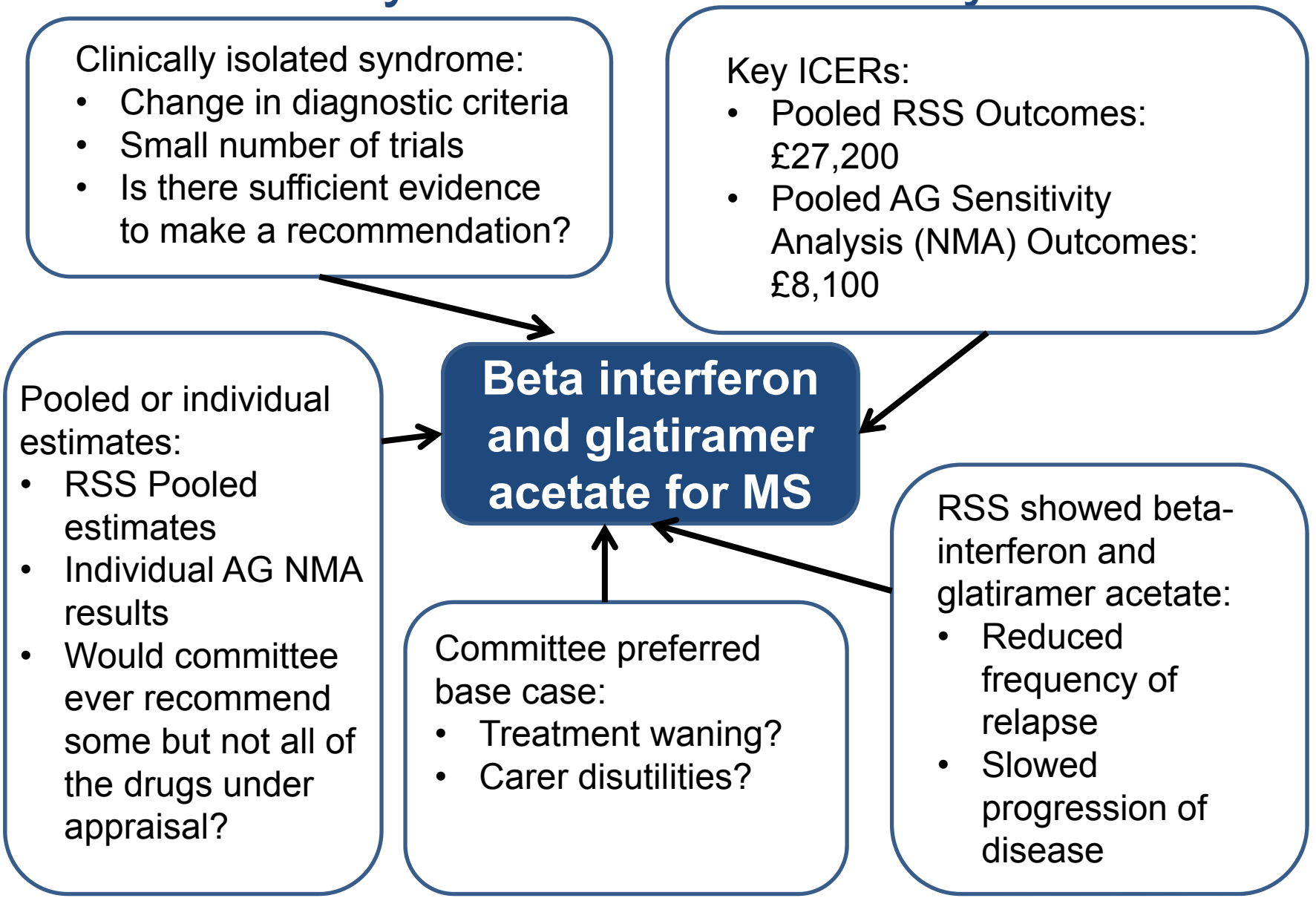
Lead team presentation

Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32)

1st Appraisal Committee meeting
Committee B, 2nd November 2016

Lead team: Miriam McCarthy, Stephen Palmer and Dani Preedy
Companies: Bayer, Biogen, Merck Serono, Novartis, Teva
Chair: Amanda Adler
Assessment group: Warwick Evidence
NICE technical team: Thomas Palmer, Jasdeep Hayre

Summary of evidence and key issues



Key issues

- Are beta interferon and glatiramer acetate clinically effective for RRMS? Are all the technologies equally as effective?
- Which analyses reflect clinical practice (NMA or RSS?)
- Are the trial results for clinically isolated syndrome generalisable?
- Does the committee prefer results including treatment waning effects and carer disutilities?
- Does the committee prefer the treatment effectiveness estimates from the risk sharing scheme or from the assessment group meta-analysis?
- Innovation
- Equalities
- PPRS

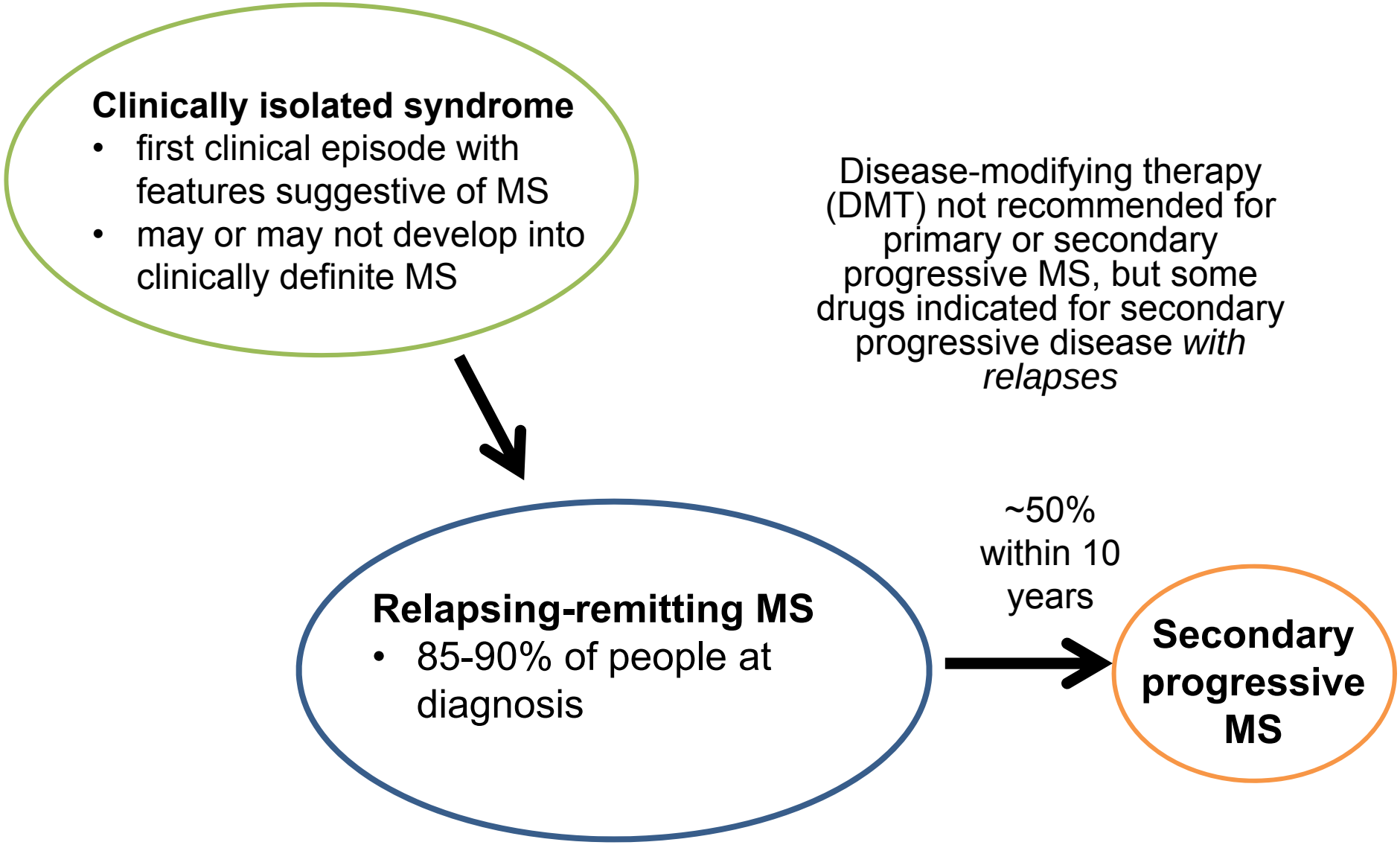
Multiple sclerosis and clinically isolated syndrome

- Multiple sclerosis (MS) is a chronic, neurodegenerative disorder which affects the brain, optic nerves, and spinal cord
- It often results in progressive neurological impairment and severe disability
- Associated with symptoms such as pain, disturbance to muscle tone, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment
- Approximately 100,000 people in the UK have MS, and about 2500 people are newly diagnosed each year
- Onset typically between 20 and 50 years
- A single demyelinating event before MS is known as clinically isolated syndrome (CIS)
  - definition of clinically isolated syndrome (CIS) was revised in 2010 update of the diagnostic criteria

Patient and professional feedback

- These treatments have been shown to be effective in reducing relapses and slowing the progression of MS
- They have formed an integral part of current practice since the establishment of the risk sharing scheme
- There is a lot of experience of using these drugs and the safety profiles are therefore more certain than for newer treatments which can be an important consideration for patients
- Choice of administration, both in terms of frequency and method, is important. The greater the range of disease modifying therapies available the more people that are likely to find the treatment that suits them
- There are currently no other treatment options licensed for clinically isolated syndrome

Multiple sclerosis



Current management of MS

1st line

RRMS

- Interferon beta?
- Glatiramer acetate?
- Teriflunomide (TA303)
- Dimethyl fumarate (TA320)
- Alemtuzumab (TA312)

CIS

- Interferon beta?
- Glatiramer acetate?
- Disease modifying therapies

Rapidly-evolving severe

- Natalizumab (TA127)
- Alemtuzumab (TA312)

Change therapy – inadequate response/ adverse events

2nd line

- Teriflunomide
- Dimethyl fumarate
- Alemtuzumab

Highly active disease

- Fingolimod (TA 254)
- Alemtuzumab (TA312)

Technologies

- Beta interferons: work by reducing the inflammatory process that characterises MS
  - There are two types of recombinant IFN-β: IFN β-1a and IFN β-1b
- Glatiramer acetate: work by reducing the inflammation around nerves. Glatiramer is an acetate salt of polypeptides formed from the synthesis of four amino acids. It resembles myelin, the basic protein that is found in the sheath surrounding nerve
- Exact mode of action for both are relatively unknown

Technologies – Summary

	IFN β-1a			IFN β-1b		Glatiramer
	Avonex	Rebif	Plegridy	Betaferon	Extavia	Copaxone
RRMS	✓	✓	✓	✓	✓	✓
SPMS	✗	✗	✗	✓	✓	✗
CIS	✓	✓	✗	✓	✓	✗
Dose	30 mcg	44 or 22 mcg	125mcg	250mcg	250mcg	20mg or 40mg
Admin	IM	SC	SC	SC	SC	SC
Freq.	Weekly	3 times per week	Every 2 weeks	Every other day	Every other day	Daily or 3/week
Cost pppy	£8,502	£7,976 or £10,572	£8502	£7,264	£7,264	£6,681-£6,704

RRMS: Relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; CIS: clinically isolated syndrome; pppy: per person per year; IM: intramuscular; SC: subcutaneous

Technologies – interferon beta-1a

	Avonex (Biogen)	Rebif (Merck)	Plegridy (Biogen)
Indication	• RRMS – in clinical trials ≥2 acute exacerbations in past 3 years without evidence of continuous progression • Clinically isolated syndrome • Discontinue if patients develop progressive MS	• RRMS – in clinical trials ≥2 acute exacerbations in past 2 years • Clinically isolated syndrome • Refib 22 not licensed for CIS	• RRMS in clinical trials ≥2 acute exacerbations in past 3 years Note: Plegridy is a pegylated IFN β-1a
Dosage	30 mcg intramuscular injection per week	44 mcg or 22 mcg subcutaneous injection 3 times per week	125 mcg subcutaneous injection every 2 weeks
Cost (list price)	£8,502 per person per year	£7,976/£10,572 per person per year	£8,502 per person per year

Technologies – interferon beta-1b and glatiramer acetate

IFN β-1b

Glatiramer

	Betaferon	Extavia	Copaxone
Indication	• RRMS – in clinical trials >2 acute exacerbations in past 2years • Clinically isolated syndrome (if it is severe enough to warrant IV corticosteroid) • Patients with SPMS with active disease, evidenced by relapses.		• RRMS – in clinical trials ≥2 acute exacerbations in past 2 years
Dosage	250 mcg subcutaneous every other day		20 mg daily or 40 mg three times a week subcutaneous injection.
Cost (list price)	~£7,264 per person per year		£6,704/£6,681 per person per year for 20mg/40mg

History of this appraisal and NICE guidance

Previous Appraisals

Beta interferon (Rebif, Avonex, Betaferon) and glatiramer acetate (Copaxone)
TA32, Jan 2002
- Not recommended

DoH Risk sharing scheme (RSS)
- Price reduction or company contribution to NHS costs (3 of the 4 products)
- Data collection on clinical outcomes

RSS Ended 2016

Current Appraisal

1st meeting TODAY
- Long term outcome data from risk sharing scheme now available

New products
- Interferon 1b (Extavia, Novartis)
- Pegylated interferon beta 1a (Plegridy, Biogen)
- New formulation glatiramer acetate (Copaxone, Teva)

Risk Sharing Scheme

- Original appraisal found DMTs cost-effective at a threshold of £36,000 per QALY when evaluated over a 20 year time horizon
- Treatment effects were based on RCTs with median follow-up ~2 years and NICE were unwilling to extrapolate these effects over such a long horizon
- Department of Health set up a risk-sharing scheme (RSS) to provide interferon β-1a (Avonex, Rebif), interferon β-1b (Betaferon) and glatiramer (Copaxone) to patients
- The RSS was established to monitor whether the DMTs continued to demonstrate treatment effects comparable to the RCTs
- An economic model was produced using the data from the RSS
- The intention: if the observed benefits of treatment fell below those estimated in the model, a new cost-effective price would be established
- Anyone with relapsing remitting MS, or with secondary progressive MS in which relapses remain a dominant feature & meet criteria from the Association of British Neurologists were eligible
- Confidential discounts and contributions
  - <<For this presentation list-prices are used: wording tbc pending ongoing correspondence>>

Risk Sharing Scheme - Outcomes

- Primary outcome measure used in the RSS is a summary measure of disease progression for the patients recruited to the scheme
- Adjustments to prices were calculated on the basis of any deviation between the actual outcomes for patients in the RSS cohort and the “target outcomes” predicted on the basis of the original model
- This requires calculation of the “implied hazard ratio” – the hazard ratio which implies zero deviation from the target
- Progression rates with treatment are then calculated in the RSS economic model by multiplying the instantaneous natural history progression rates by these implied hazard ratios

Submissions

Submissions:

- Biogen – interferon beta-1a (Avonex) and pegylated interferon beta-1a (Plegridy)
- Merck - interferon beta-1a (Rebif)
- Teva – glatiramer acetate (Copaxone)

Non-submissions:

- Bayer – interferon beta-1b (Betaferon)
- Novartis – interferon beta-1b (Extavia)

Assessment group's report:

- Clinical evidence review
- Pooled RSS data

Decision problem - **population**

Company submissions compared to NICE scope

NICE scope population	• People with relapsing remitting multiple sclerosis (including people with relapsing remitting multiple sclerosis and people with secondary progressive multiple sclerosis with active disease, evidenced by relapses) • People with clinically isolated syndrome, that is, a single demyelinating event, who are considered at high risk of developing multiple sclerosis
Biogen	• Treatment should be discontinued in patients who develop progressive MS • Patients with CIS are not considered in the economic model
Merck	Commented that the RSS model didn't separate RRMS and SPMS
Teva	Patients with CIS are not considered in economic model

Decision problem – **comparators and outcomes**

Company submissions compared to NICE scope

NICE Scope Comparator	• Best supportive care without disease modifying treatment • If appropriate, the beta interferons and glatiramer acetate will be compared with each other
Biogen	As per scope: best supportive care considered to include placebo
Merck	As per scope
Teva	As per scope
NICE Scope Outcomes	• Relapse rate • Severity of relapse • Disability (for example, expanded disability status scale [EDSS]) • Symptoms of multiple sclerosis such as fatigue, cognition and visual disturbance • Freedom from disease activity • Presence of neutralising antibodies • Mortality • Adverse effects of treatment • Health-related quality of life
Biogen	As per scope
Merck	As per scope
Teva	As per scope

Assessment group's critique of company NMAs

Biogen	Merck	Teva
• Quality of NMA reasonable and appropriate • Inputs for NMA model "opaque" • Decision to stratify estimates by 12 or 24 months not clearly explained • Exclusions based on follow-up not explicitly stated	• Quality of NMA reasonable and appropriate • Several relevant trials were not included • Company submission included trials of patients with PRMS, which was outside of the NICE scope • NMAs not presented for CIS or SPMS • Outcomes for TTP3 and TTP6 combined in same analysis	• Quality of NMA reasonable and appropriate • Lack of transparency about inputs for each NMA model • Not clear how dosages were used in the included models • NMAs not presented for CIS
• **Assessment group did their own pairwise and network meta-analyses…**		

TTP3/6: time to disease progression 3/6 months; PRMS: Progressive-relapsing multiple sclerosis

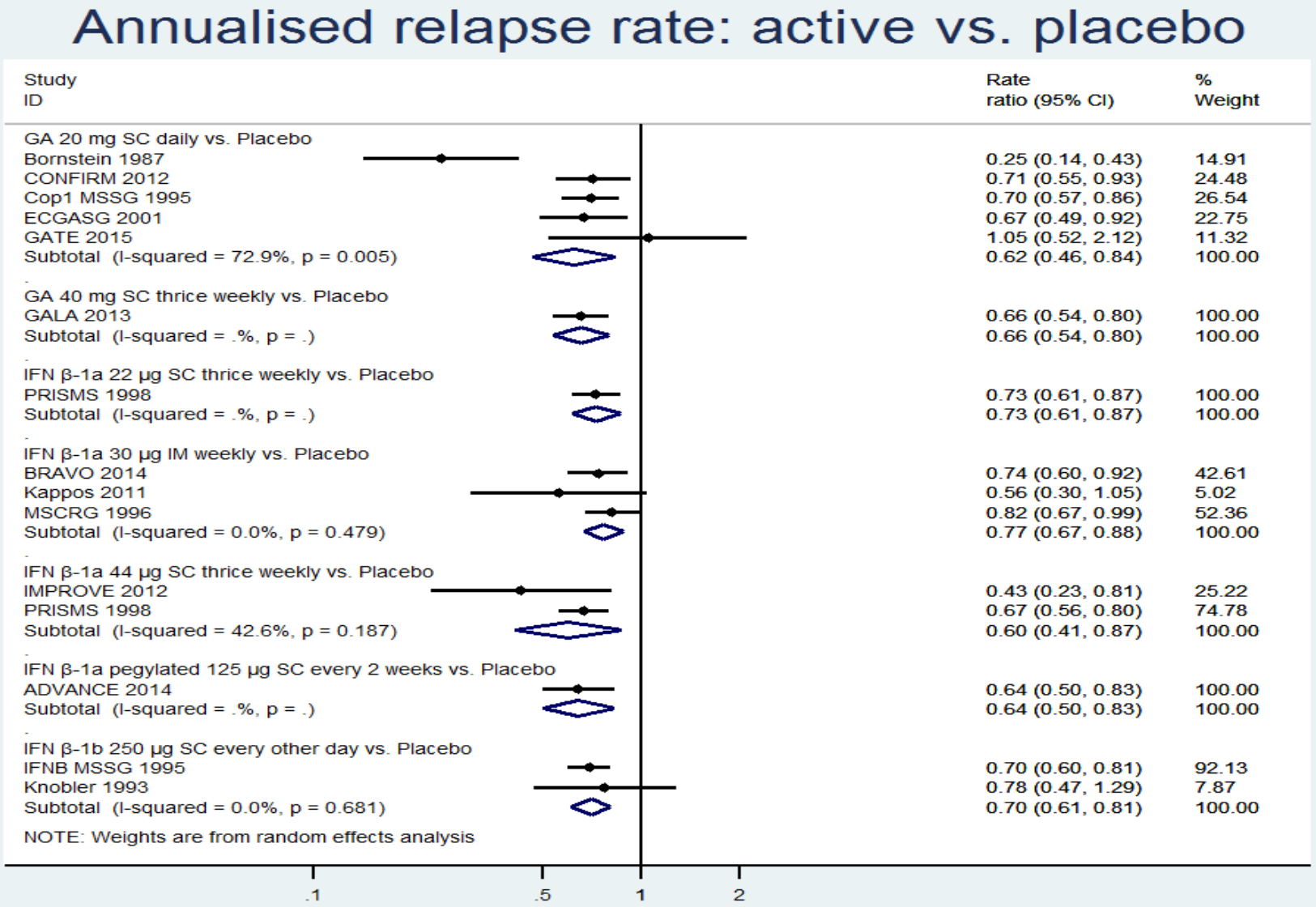
Companies' network meta-analyses RRMS – treatments compared to placebo

Drug (estimates provided by respective manufacturer)	Company TTP3	Company ARR	Company TTP6
IFN β-1a pegylated 125 µg every 2 weeks	0.62 (0.21, 1.85)	0.64 (0.41, 1.04)	0.46 (0.12, 1.77)
Glatiramer (company did not specify dosage)	[redacted]	[redacted]	[redacted]
IFN β-1a 44 µg SC thrice weekly	0.74*(0.51, 1.05)	0.67* (0.6, 0.74)	0.7 (0.47, 1.01)*
IFN β-1a 22 µg SC thrice weekly	0.74*(0.46, 1.19)	0.71*(0.62, 0.81)	0.72*(0.43, 1.18)
IFN β-1a 30 µg IM weekly	0.73 (0.31, 1.72)	0.78 (0.60, 0.98)	0.73 (0.20, 2.69)

NB: Results are those of each respective manufacturer. Neither manufacturer of IFN β-1b made a submission. Results marked * are median (95% CrI), all others mean (95% CrI).

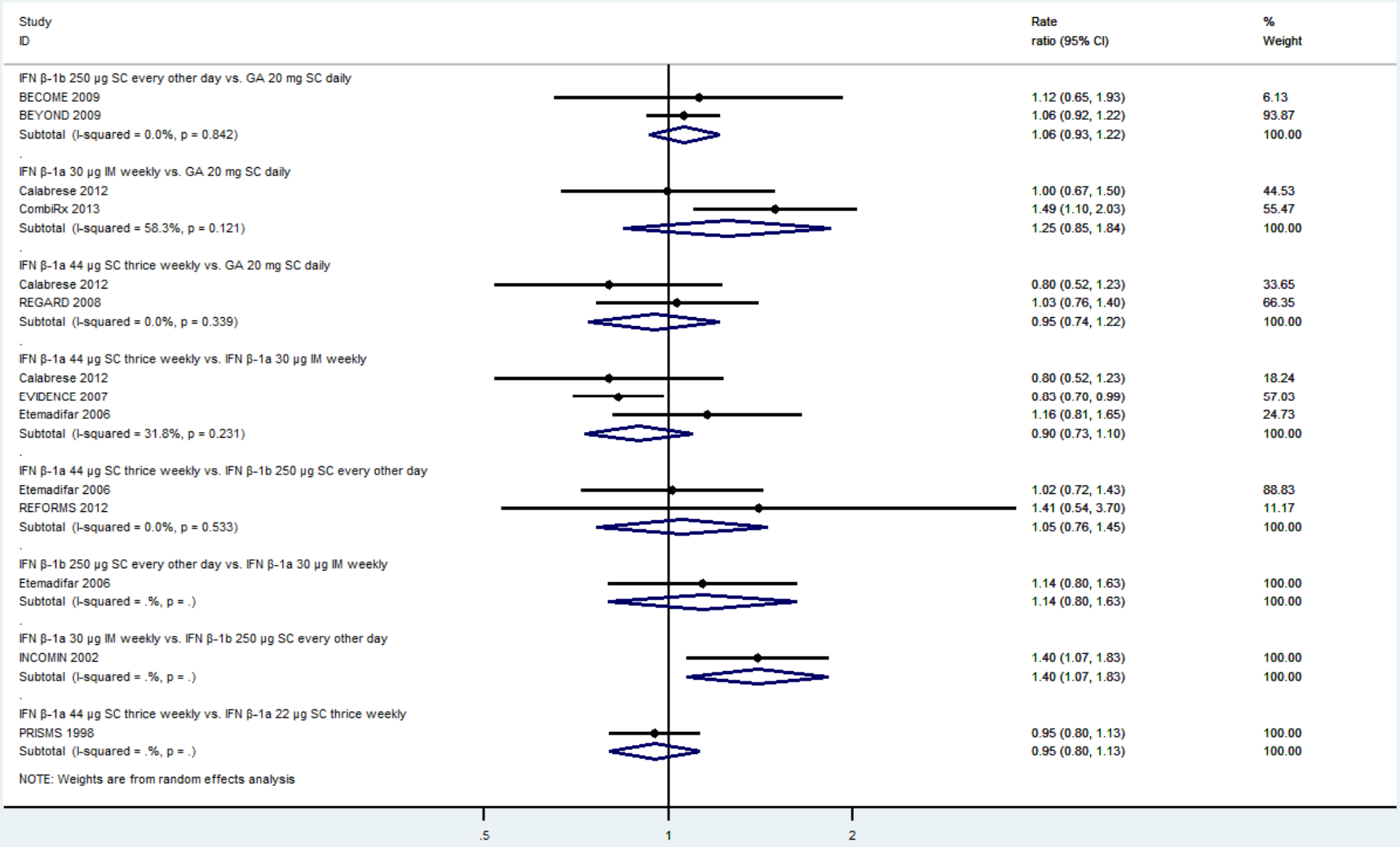
ARR: annualised relapse rate; TTP3/6: time to disease progression 3/6 months; RR: rate ratio; HR: hazard ratio

Assessment group pairwise meta-analysis



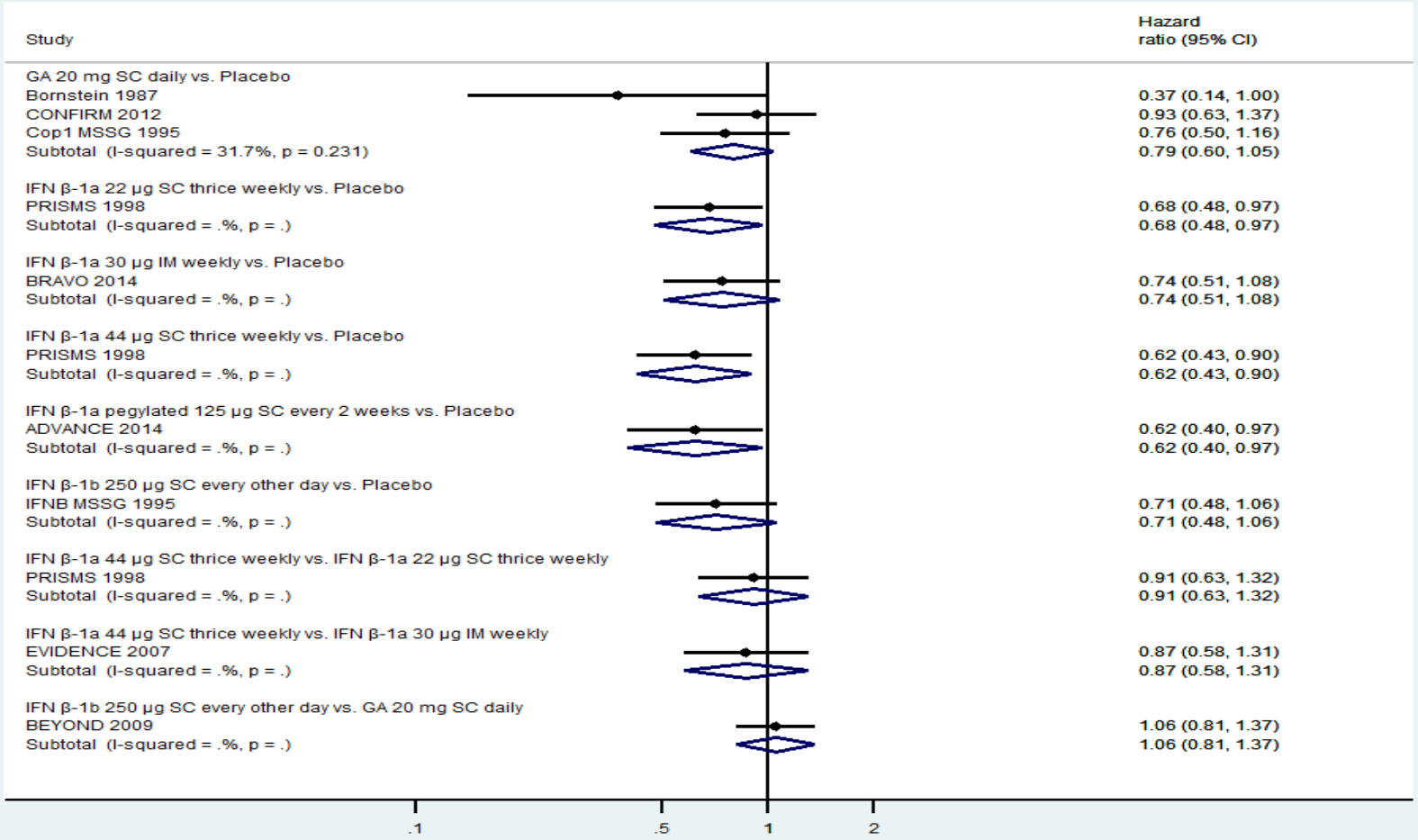
Assessment group pairwise meta-analysis

Annualised relapse rate: active vs. active

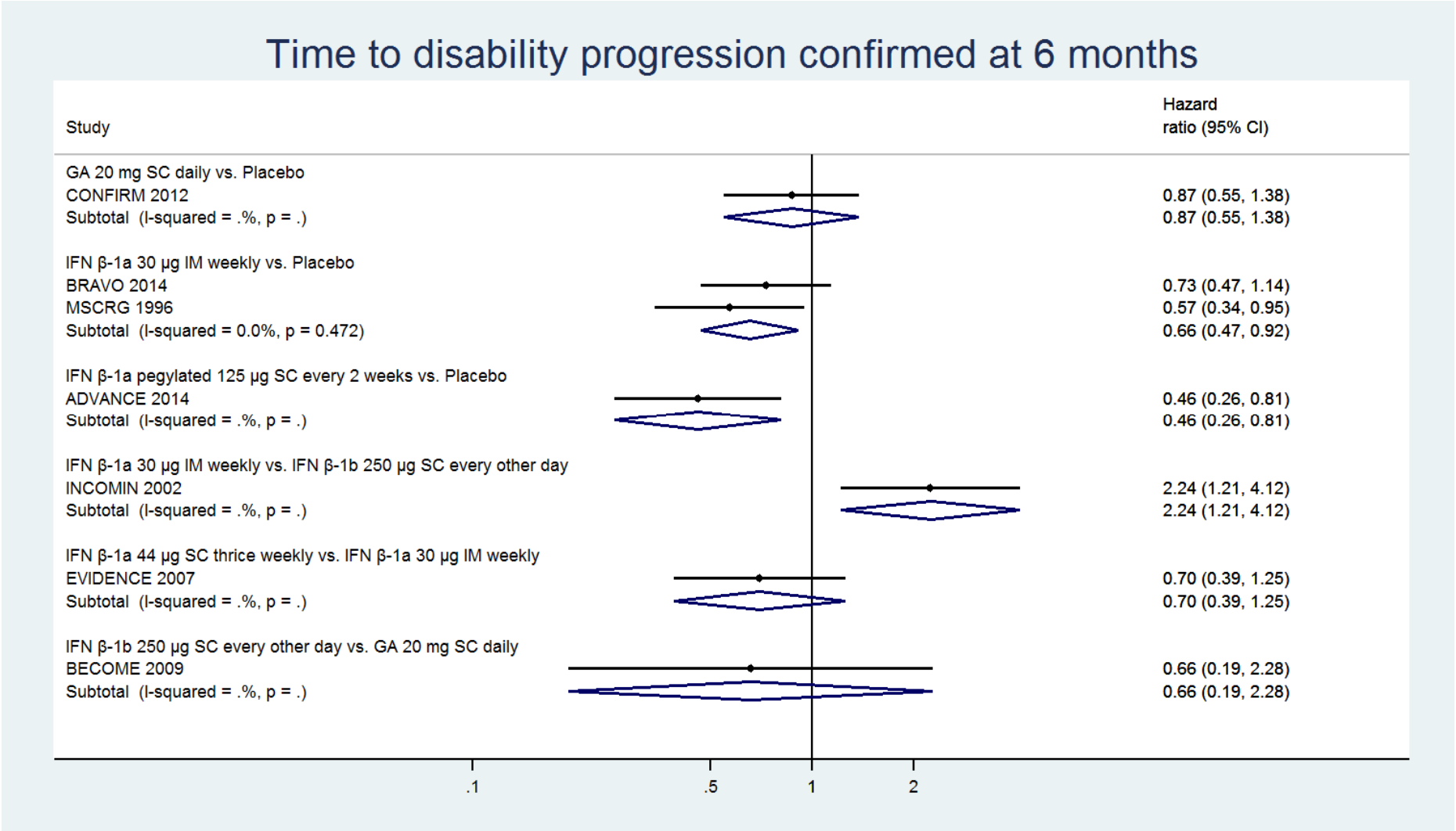


Assessment group pairwise meta-analysis

Time to disability progression confirmed at 3 months

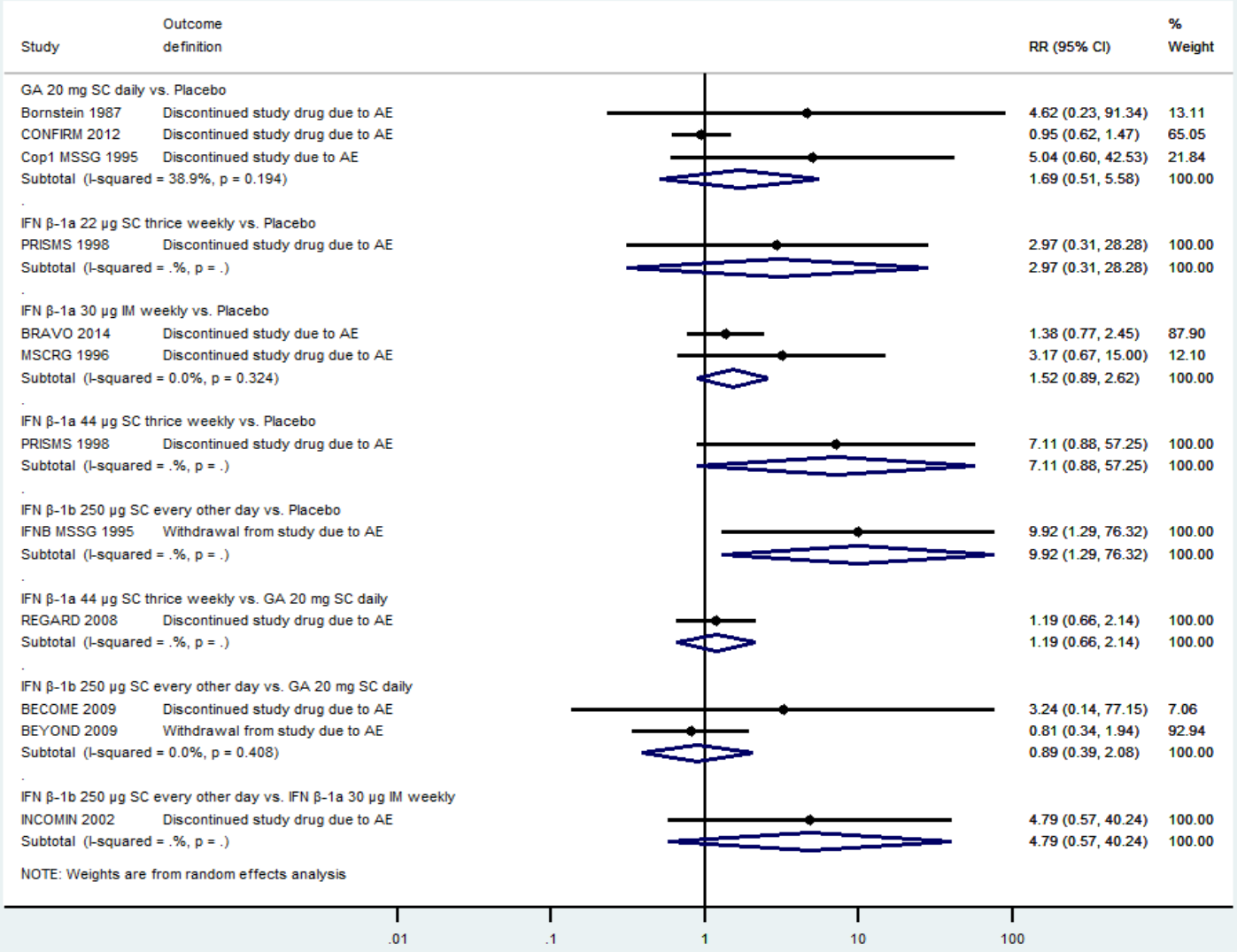


Assessment group pairwise meta-analysis

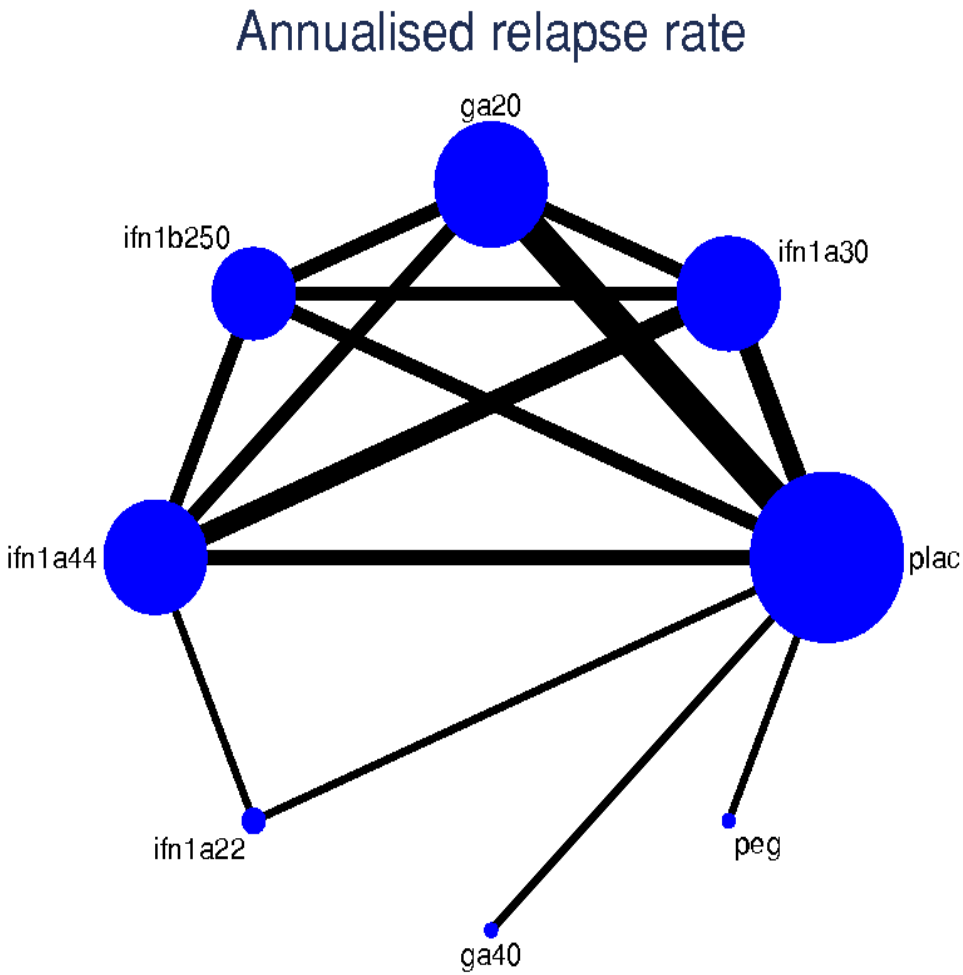


Assessment group's meta-analysis RRMS

Discontinuation due to AEs: 24 months



Assessment groups network meta-analysis



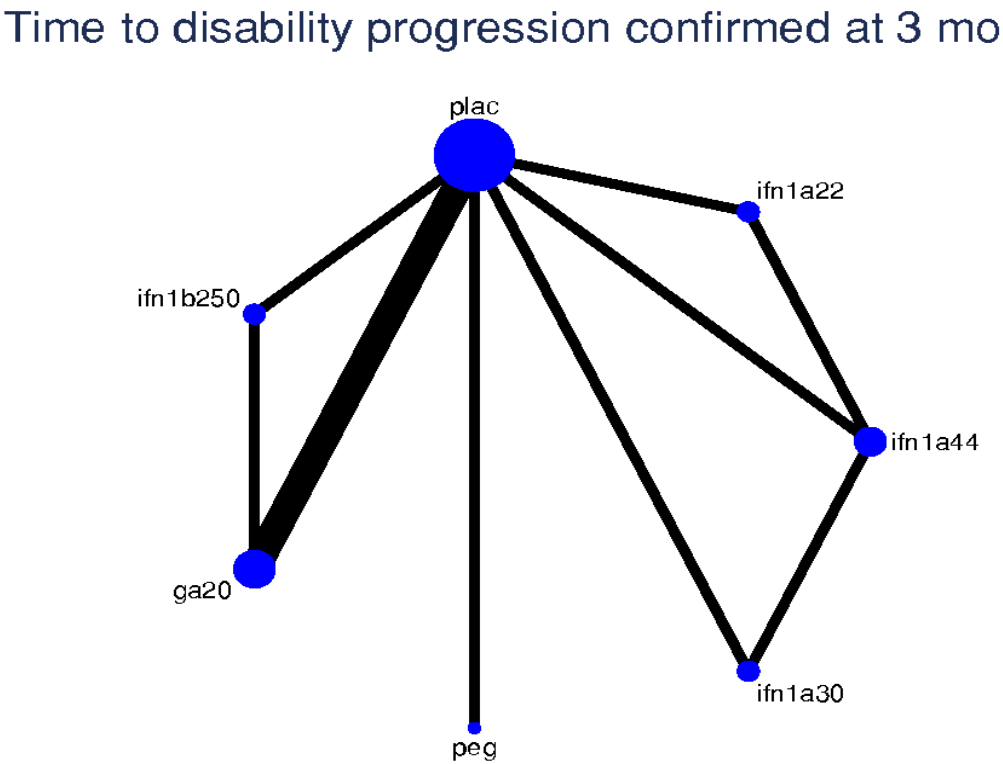
ifn1a30: IFN β-1a 30 mcg IM once a week; ifn1a44: IFN β-1a 44 mcg SC three times weekly; ifn1a22: IFN β-1a 22 mcg SC three times weekly; ifn1b250: IFN β-1b 250 mcg SC every other day; peg: IFN β-1a pegylated 125 mcg SC every two weeks; ga20: GA 20 mg SC once daily; ga40: GA 40 mg SC thrice weekly; plac: placebo

Assessment Group network meta-analysis – RRMS ARR

Drug	GA 20 mg	IFN β-1a pegylated 125 mcg	GA 40 mg	IFN β-1a 44 mcg	IFN β-1b 250 mcg	IFN β-1a 22 mcg	IFN β-1a 30 mcg	Placebo
GA 20 mg		0.98 (0.71, 1.35)	0.95 (0.73, 1.25)	0.94 (0.71, 1.24)	0.92 (0.70, 1.21)	0.89 (0.66, 1.20)	0.80 (0.61, 1.05)	0.64 (0.50, 0.83)
IFN β-1a pegylated 125 mcg			0.97 (0.78, 1.21)	0.96 (0.77, 1.20)	0.94 (0.75, 1.17)	0.91 (0.70, 1.17)	0.82 (0.65, 1.02)	0.66 (0.54, 0.80)
GA 40 mg	-			0.99 (0.87, 1.12)	0.98 (0.86, 1.12)	0.93 (0.78, 1.12)	0.84 (0.74, 0.95)	0.68 (0.61, 0.75)
IFN β-1a 44 mcg					0.98 (0.86, 1.12)	0.94 (0.80, 1.11)	0.85 (0.76, 0.95)	0.68 (0.61, 0.76)
IFN β-1b 250 mcg						0.96 (0.80, 1.15)	0.87 (0.77, 0.98)	0.70 (0.63, 0.77)
IFN β-1a 22 mcg							0.90 (0.76, 1.07)	0.72 (0.62, 0.85)
IFN β-1a 30 mcg								0.80 (0.73, 0.89)

Results presented as rate ratio (95% CI) and exclude Bornstein (1987) as it is a statistical outlier. ARR: Annualised relapse rate

Assessment groups network meta-analysis



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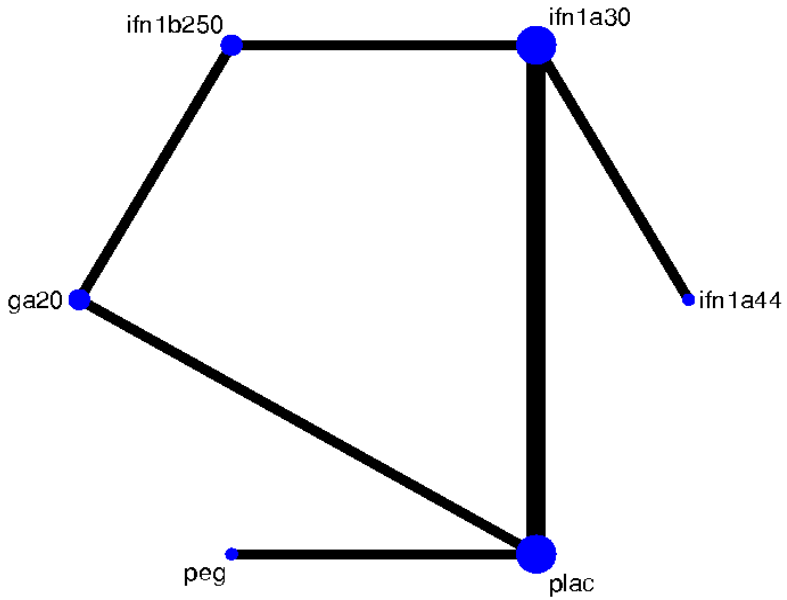
Assessment Group network meta-analysis – RRMS TTP3

Drug	IFN β-1a 44 µg	IFN β-1a pegylated 125 µg	IFN β-1a 22 µg	IFN β-1a 30 µg	GA 20 mg	IFN β-1b 250 µg	Placebo
IFN β-1a 44 µg		1.01 (0.59, 1.74)	0.92 (0.65, 1.30)	0.86 (0.62, 1.19)	0.82 (0.56, 1.22)	0.81 (0.53, 1.22)	0.63 (0.46, 0.86)
IFN β-1a pegylated 125 µg			0.91 (0.52, 1.59)	0.85 (0.49, 1.46)	0.81 (0.49, 1.34)	0.80 (0.47, 1.34)	0.62 (0.40, 0.97)
IFN β-1a 22 µg				0.94 (0.62, 1.42)	0.90 (0.59, 1.36)	0.88 (0.57, 1.36)	0.68 (0.49, 0.96)
IFN β-1a 30 µg					0.96 (0.65, 1.42)	0.94 (0.62, 1.43)	0.73 (0.53, 1.00)
GA 20 mg						0.98 (0.78, 1.24)	0.76 (0.60, 0.97)
IFN β-1b 250 µg							0.78 (0.59, 1.02)

Results presented as hazard ratio (95% CI). TTP3: time to disability progression confirmed at 3 months

Assessment groups network meta-analysis

Time to disability progression confirmed at 6 months



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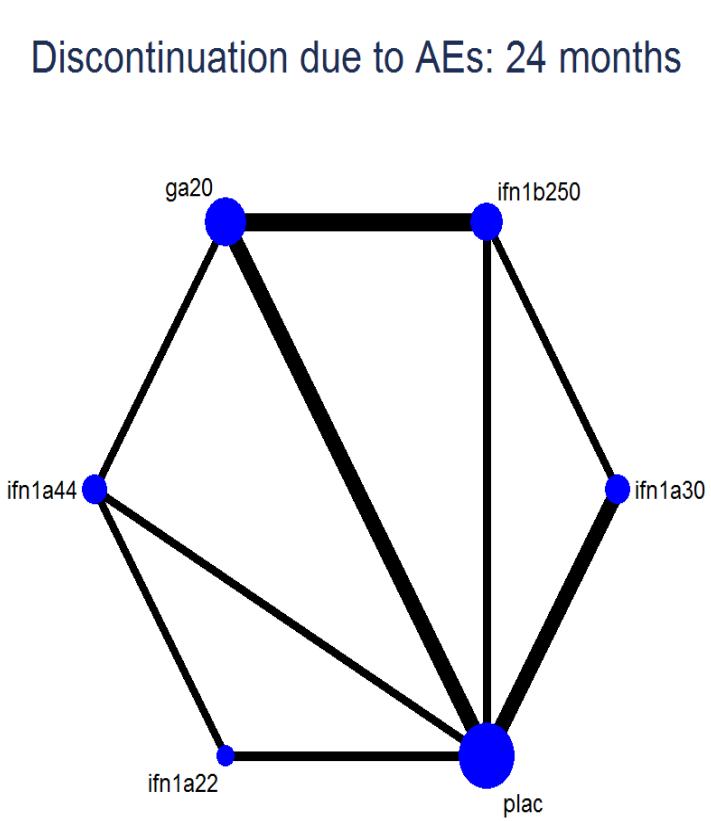
Assessment Group network meta-analysis – RRMS TTP6

Drug	IFN β-1b 250 µg	IFN β-1a pegylated	IFN β-1a 44 µg	IFN β-1a 30 µg	Glatiramer 20 mg	Placebo
IFN β-1b 250 µg		0.74 (0.32, 1.71)	0.71 (0.32, 1.60)	0.50 (0.29, 0.87)	0.42 (0.21, 0.83)	0.34 (0.18, 0.63)
IFN β-1a pegylated 125 µg			0.97 (0.40, 2.33)	0.68 (0.35, 1.31)	0.56 (0.28, 1.15)	0.46 (0.26, 0.81)
IFN β-1a 44 µg				0.70 (0.39, 1.25)	0.58 (0.27, 1.27)	0.47 (0.24, 0.93)
IFN β-1a 30 µg					0.83 (0.49, 1.41)	0.68 (0.49, 0.94)
Glatiramer 20 mg						0.82 (0.53, 1.26)

Results presented as hazard ratio (95% CI). TTP6: time to disability progression confirmed at 6 months

Assessment groups network meta-analysis RRMS



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Assessment group's network meta-analysis RRMS – discontinuation due to AEs at 24 months

Drug	IFN β-1b 250 mcg	IFN β-1a 44 mcg	Glatiramer 20 mg	IFN β-1a 22 mcg	IFN β-1a 30 mcg	Placebo
IFN β-1b 250 mcg		1.15 (0.20, 6.56)	1.70 (0.50, 5.81)	2.37 (0.22, 25.84)	2.74 (0.56, 13.38)	4.41 (1.07, 18.29)
IFN β-1a 44 mcg			1.48 (0.39, 5.57)	2.07 (0.32, 13.44)	2.39 (0.38, 15.22)	3.85 (0.81, 18.29)
Glatiramer 20 mg				1.40 (0.17, 11.76)	1.61 (0.38, 6.91)	2.60 (0.88, 7.64)
IFN β-1a 22 mcg					1.15 (0.10, 13.09)	1.86 (0.21, 16.83)
IFN β-1a 30 mcg						1.61 (0.52, 5.02)

NB: Results are presented as risk ratios with 95% CI

Clinically isolated syndrome: New diagnostic criteria

- The definition of clinically isolated syndrome (CIS) was revised in the 2010 update of the diagnostic criteria, and diagnosis of MS can occur after a single neurological event with supporting magnetic resonance imaging (MRI) results.
- Prior to these changes, CIS accounted for approximately 2-3% of the overall MS population but the figure will now be lower
- CIS studies prior to 2010 would therefore include some patients who would now have a clinical diagnosis of MS
- The “CIS” population in this analysis therefore represents a mix of early MS and true

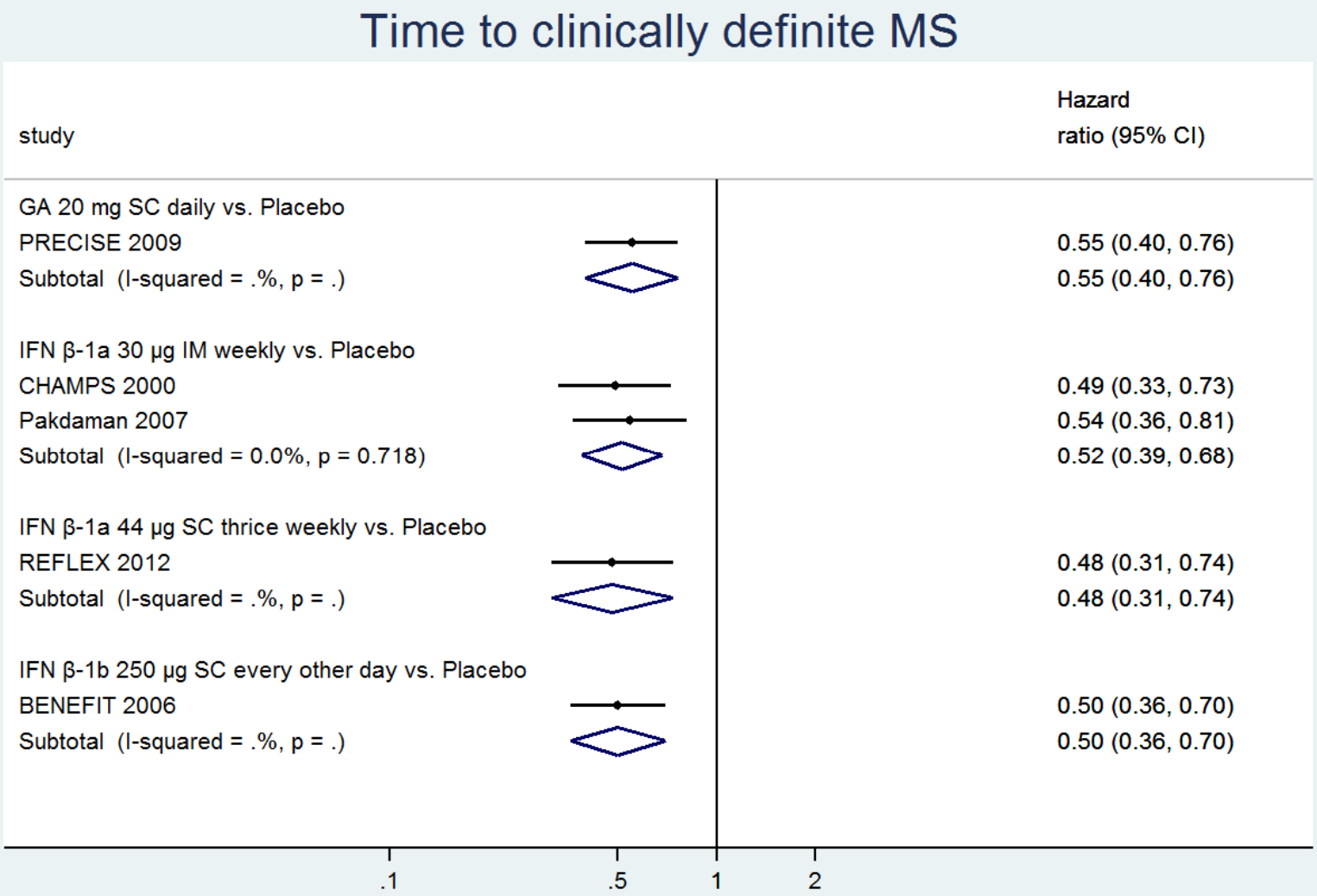
⊙ *Are the clinically isolated syndrome results relevant to current practice?*

Clinically Isolated Syndrome: Assessment group's network meta-analysis included studies

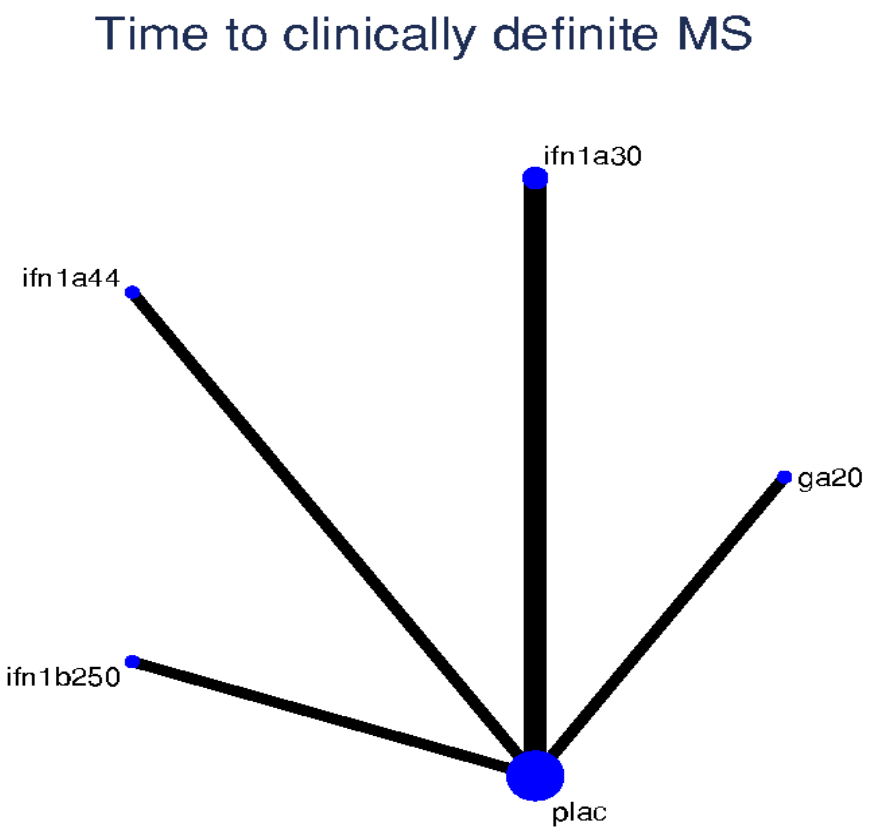
Study	Drug (vs. placebo)	Follow-up (months)	Treatment (N)	Treatment AEs (N(%))	Control (N)	Control AEs (N(%))
PreCISe 2008	GA 20 mg daily	36	243	14 (5.8%)	238	4 (1.7%)
REFLEX 2012	IFN β-1a 44 mcg SC thrice weekly	24	171	5 (2.9%)	171	6 (3.5%)
CHAMPS 2000	IFN β-1a 30 mcg IM weekly	36	193	1 (0.5%)	190	7 (3.7%)
BENEFIT 2006	IFN β-1b 250 mcg SC every other day	24	292	24 (8.2%)	176	1 (0.6%)

NB: The companies did not include CIS in their NMAs. AEs: adverse events.

Assessment group pairwise meta-analysis



Assessment groups network meta-analysis
CIS – network diagram



ifn1a30: IFN β-1a 30 mcg IM once a week; ifn1a44: IFN β-1a 44 mcg SC three times weekly; ifn1b250: IFN β-1b 250 mcg SC every other day; ga20: GA 20 mg SC once daily; plac: placebo

AG network meta-analysis CIS

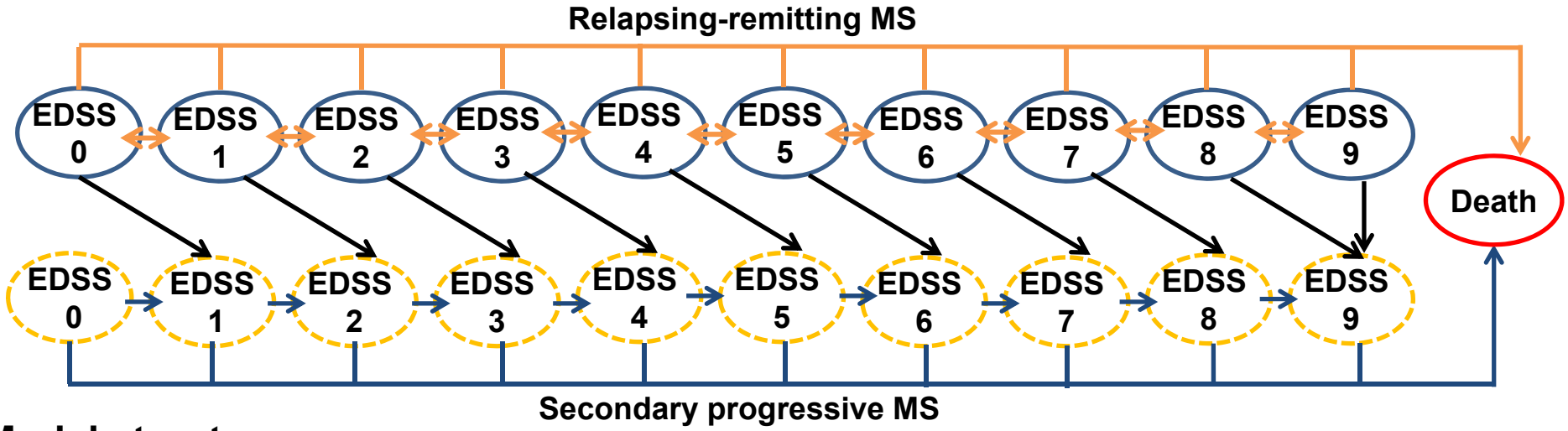
Time to clinically definite MS

Drug	IFN β-1b 250 mcg SC every other day	IFN β-1a 30 mcg IM weekly	Glatiramer 20 mg daily	Placebo
IFN β-1a 44 mcg SC thrice weekly	0.96 (0.56, 1.65)	0.93 (0.56, 1.55)	0.87 (0.51, 1.50)	0.48 (0.31, 0.74)
IFN β-1b 250 mcg SC every other day		0.97 (0.63, 1.50)	0.91 (0.57, 1.45)	0.50 (0.36, 0.70)
IFN β-1a 30 mcg IM weekly			0.94 (0.61, 1.45)	0.52 (0.39, 0.68)
Glatiramer 20 mg daily				0.55 (0.40, 0.76)

NB: Findings expressed as HR (95% CI). The companies did not provide a NMA for CIS

Cost effectiveness

Risk Sharing Scheme Model (RRMS)



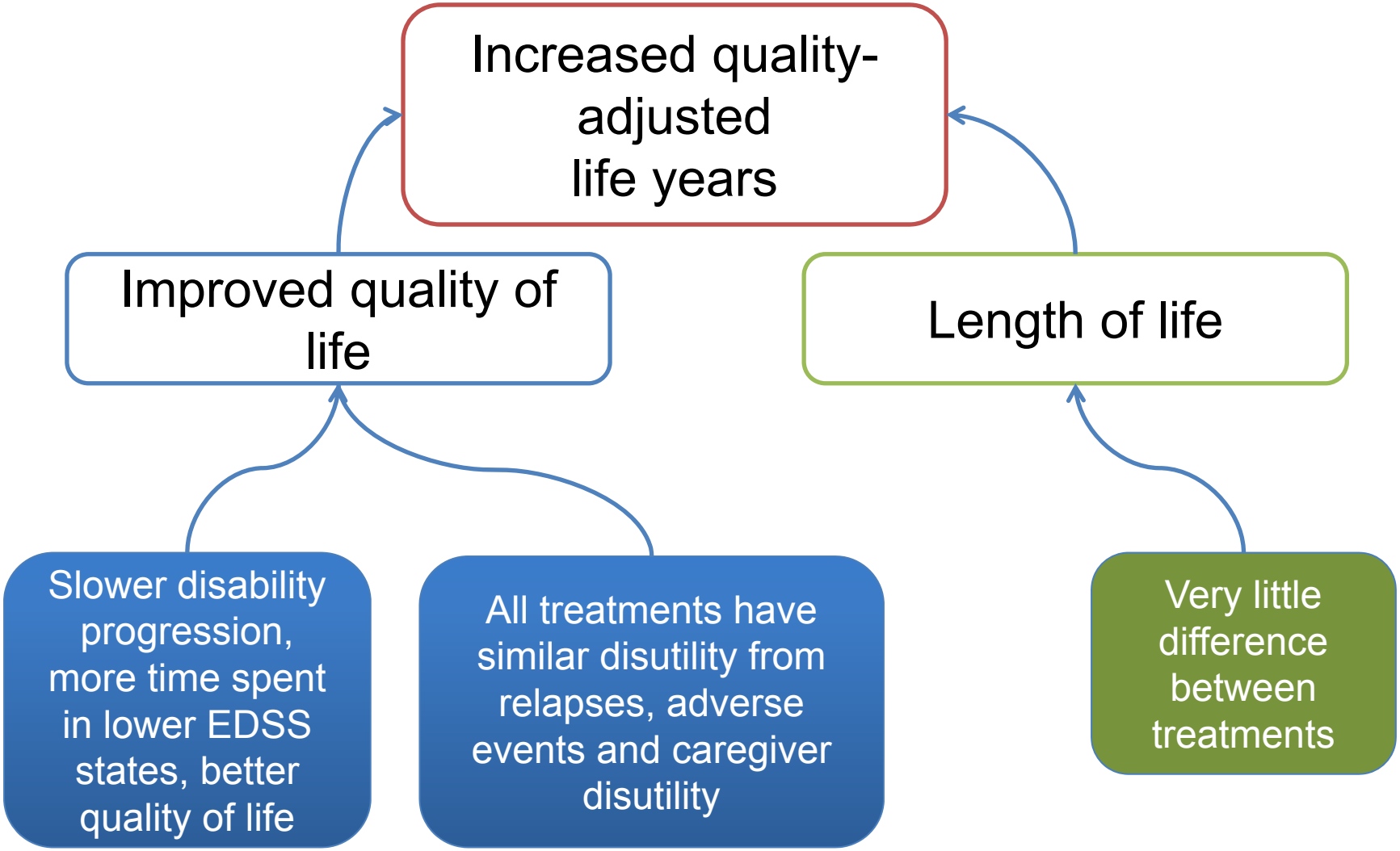
Model structure

- Cohort based Markov model
- Health states for people with RRMS or secondary progressive multiple sclerosis (SPMS) were characterised by EDSS levels ranging from 0-10
- People are able to progress to more severe EDSS levels, regress to less severe EDSS levels, or there is a probability of dying from MS-related or other causes
- Information required on the natural history of people with RRMS was based on the British Columbia multiple sclerosis (BCMS) cohort

Model Assumptions

- Cycled yearly
- Starting age 30 years
- 50-year time horizon
- 3.5% discount rate for costs and utilities
- MS-related death for people in EDSS 7-9 only

How treatments increase QALYs in model: RRMS



Risk Sharing Scheme Model Inputs

Parameter	Value	Source
Annual discontinuation	0.05	RSS data collection
Annual relapse rate (RR [95% CI])	0.72 (NR)	MS Trust Survey 2002
'Implied' Progression HR (95% CI)	0.79 (0.77, 0.81)	RSS assumption (see slide 14)

- The RSS pooled results for all treatments when collecting data
- Combined treatment effect of:
  - IFN β-1a 44 or 22 mcg SC 3 times a week (Rebif)
  - GA 20 mg SC daily (Copaxone)
  - IFN β-1b 250 mcg SC every other day (Betaferon)
  - IFN β-1a 30 mcg IM weekly (Avonex)

⊙ *Are beta interferon and glatiramer acetate clinically effective? Are they equally as effective for RRMS?*

⊙ *Which analyses reflect clinical practice (NMA or RSS?)*

Assessment Group and Company Models

All models submitted shared same overall structure and were broadly similar to the RSS model

- Data sources for each submission differed
- Assessment group had concerns over the total QALYs in companies' submissions.
- Assessment group and RSS analysis estimated a mean of approximately 8.5 QALYs for best supportive care in the base case analysis
- Teva ([redacted] QALYs) and Merck ([redacted] QALYs) estimated less
- All other parameters were comparable between the models

Assessment group changes to assumptions:

- Exclusion of carers' disutilities in base case
- Changes to mortality assumptions to avoid double counting

Company Economic Submissions Summary

Parameter	Biogen	Merck	Teva
Natural history cohort	Natural history cohort based on extrapolating the ADVANCE placebo arm data with British Columbia cohort	Natural history cohort based on British Colombia natural history model.	British Columbia dataset was used for RRMS transitions. London Ontario data was only used for RRMS to SPMS and SPMS transitions
Population	Adults (≥ 18 years) with RRMS	Adults with RRMS, SPMS and CIS	Adults (≥ 18 years) with RRMS
Intervention	All INFβs and glatiramer	Rebif only (INFβ-1a 44mcg or 22mcg)	All INFβs and glatiramer For 2nd line therapy: • Gilenya 500mg • Tysabri 300mg • Tecfidera 240mg
Comparator	Best supportive care	CIS: Best supportive care for CIS and DMDs for RRMS. RRMS & SPMS: Best supportive care	Best supportive care
Time horizon	50 years	50 years	50 years

Company Economic Submissions Summary

Parameter	Biogen	Merck	Teva
Type of model and health states	• Cohort based Markov model • 21 health states (10 for RRMS, 10 for SPMS and dead) • EDSS levels 0-10 with increments of 0.5	RRMS + SPMS: • Cohort based Markov model • 21 health states: (10 for on treatment, 10 for no treatment and dead) • EDSS levels 0-9, with increments of 1.0 CIS: • Additional 5 on treatment and 5 off treatment health states defined by EDSS levels 0-5	• Cohort based Markov model • 21 health states (10 for RRMS, 10 for SPMS and dead) • EDSS levels ranging 0-10 with increments of 1
Hazard ratio	Year 10 implied HR of [redacted] for IM IFNβ-1a 30mcg. HRs based on confirmed disability progression.	RRMS HRs supplied to Merck by DH based year 10 RSS data. (Progression HR (44mcg): [redacted], HR (22mcg): [redacted]Relapse HR (44mcg): 0.67, HR (22mcg): 0.71) • SPSMS HRs derived from SPECTRIMS • CIS conversion rate based on REFLEX	[redacted] for disability progression [redacted]derived from 10 year RSS. [redacted]from NMA

Company Economic Submissions Summary

Parameter	Biogen	Merck	Teva
Resource use and costs	• Drug acquisition costs • Admin costs • Monitoring costs • Relapse costs (including % hospitalised as proxy for severity) • Health state costs • Treatment-related adverse events costs	• Based on DH/ScHARR • Drug acquisition costs • Admin costs • Monitoring costs • Relapse costs • Health state costs • Treatment-related adverse events costs	• Drug acquisition costs • Admin costs • Monitoring costs • Relapse costs (including % hospitalised as proxy for severity) • Health state costs • Treatment-related adverse events costs
Health-related quality of life	• Utility by EDSS based on ADVANCE and Orme et al., 2007, which were derived from the UK MS survey • Carers' disutilities based on manufacturer's submission to NICE for TA127.	• Utility by EDSS derived by pooling data from a UK MS Trust postal survey and the Heron dataset. • Data pooled using sample size weighted averages, and undertaken by IMS Health for the MS trust.	• Utility values by EDSS level were based on Orme et al., 2007, which was derived from the UK MS survey. • Sensitivity analysis using RSS datasets. • Carers' disutilities based on manufacturer's submission to NICE for TA127.

Company Economic Submissions Summary

Parameter	Biogen	Merck	Teva
Discontinuation of treatment	• SPMS only	• EDSS state 7 • 5% stop treatment irrespective of EDSS (derived from RSS)	• EDSS state 7 • 5% stop treatment irrespective of EDSS (derived from RSS)
Relapse	• ARR from ADVANCE for EDSS≤5.5 • ARR from Patzold et al 1982 for EDSS>5.5	• Estimated from RSS	• Estimated from RSS • Distinction between moderate and severe • ARR applied to severe
Adverse events	• Adverse events reported from ADVANCE: >5% for any DMT or >3% for all treatments	• 5.1% experience adverse events every year on DMTs. • Adverse events associated with utility decrement of 0.02	• From pooled trial data • Copaxone assumed probability of AE was 0.481 • Other DMTs ranged from 0.32-0.75 • Disutility 0.004 for Copaxone
Mortality	• By EDSS level	• RSS approach: apply SMR of 2.0 to life table estimates and a MS specific mortality rate for EDSS≥6	• EDSS-dependent mortality multiplier from Teriflunomide submission applied to UK general population rates

Summary of Assessment Group model inputs

Parameters	Assessment group's source of evidence
Baseline characteristics	Risk sharing scheme
Transition probabilities	British Columbia data
Treatment effectiveness: annualised relapse rates	*Base case*: as in Risk sharing scheme *Sensitivity analyses*: from assessment group clinical review
Treatment effectiveness: time to disability progression	*Base case*: as in Risk sharing scheme *Sensitivity analyses*: from assessment group clinical review
Adverse events	Utility decrement of 0.02 associated with adverse events from disease modifying treatments. It was assumed that this decrement would only apply to the first year of commencing treatment
Discontinuation rate	*Base case*: as in Risk sharing scheme *Sensitivity analyses*: annual rates of discontinuation from assessment group clinical review

Summary of Assessment Group model inputs continued

Parameters	Assessment group's source of evidence
Mortality	• Same as that for the general population, since the risk of MS-related death is already captured in the transition matrices. (ONS 2010 in RSS)
Utility data	• MS Trust survey 2002, 2005 • Carer disutilities (not in base case): Acaster et al 2013
Costs	• Disease modifying treatment costs: BNF • Health state/EDSS costs: Kobelt et al 2000 • Cost of relapse: ScHARR 2001
Discontinuation rate	*Base case*: as in Risk sharing model (5% per annum) *Sensitivity analyses*: discontinuation rate from assessment group clinical review: combined rated of 2.29% per annum

Baseline characteristics

British Columbia	
Used in dimethyl fumarate appraisal	Improvement in EDSS allowed
n=898	Contains transitions from all states
Longitudinal dataset from MS clinic in Canada	May be subject to same limitations as London Ontario
Patients followed up 1980-1995	Contains RRMS and secondary progressive MS patients (15.7% had secondary progressive at baseline)

- RSS Model compares disability progression in the RSS cohort with the progression expected for a similar cohort of untreated patients on the basis of models estimated from a subset of patients in the British Columbia MS dataset.
- AG Model follows same approach

Model inputs: Baseline characteristics

EDSS	Age of onset below median	Age of onset above median	Total
0	61	74	135
1	295	394	689
2	411	677	1088
3	401	569	970
4	273	379	652
5	162	279	441
6	76	166	242
7	0	0	0
8	0	0	0
9	0	0	0
10	0	0	0
Total	1679	2538	4217

- In the RSS model, the population was stratified by age of onset of RRMS and by EDSS score
- Initial distribution presented in table above
- Two sets of transition probabilities were reported: transitions based on the age of onset of RRMS below (subgroup 1) and above (subgroup 2) the median age.
- These are reported on the next slides

Model Inputs

Utilities and Management Costs

EDSS State	Base Case Utility	Management Costs
0	0.9248	£1195
1	0.7614	£1195
2	0.6741	£1195
3	0.5643	£2203
4	0.5643	£2283
5	0.4906	£8045
6	0.4453	£8974
7	0.2686	£27,385
8	0.0076	£42,521
9	-0.2304	£54,055
10	0	0
Cost of relapse assumed to be £4,263 irrespective of EDSS state		

Source: RSS Model. Utilities are from the "two-pooled dataset" of MS Trust surveys (2002 and 2005)

Model Inputs

Costs of disease modifying treatments

	Cost (£, 2015)	Reference
IFN β-1a 30 mcg IM once a week	8502	British National Formulary 2015
IFN β-1a pegylated 125 mcg SC every 2 weeks	8502	
IFN β-1a 44 mcg three times per week (Rebif)	10,572	
IFN β-1b 250 mcg every other day (Betaferon)	7264	
Glatiramer acetate 40 mg three times a week with at least 48 hours apart (Copaxone)	6704	
Glatiramer acetate 20 mg SC daily (Copaxone)	6681	

Model inputs: Transition probabilities by EDSS state
Onset of MS below the median age

EDSS state	0	1	2	3	4	5	6	7	8	9	10
0	0.687	0.061	0.017	0.006	0.002	0.001	0.000	0.000	0.000	0.000	0
1	0.211	0.679	0.127	0.052	0.023	0.006	0.001	0.000	0.000	0.000	0
2	0.072	0.167	0.596	0.117	0.066	0.029	0.005	0.001	0.000	0.000	0
3	0.022	0.065	0.173	0.544	0.121	0.059	0.025	0.003	0.000	0.000	0
4	0.004	0.017	0.045	0.095	0.487	0.092	0.032	0.007	0.001	0.000	0
5	0.001	0.005	0.018	0.057	0.101	0.473	0.042	0.004	0.001	0.000	0
6	0.002	0.007	0.022	0.115	0.166	0.281	0.728	0.122	0.019	0.001	0
7	0.000	0.001	0.002	0.011	0.026	0.040	0.115	0.681	0.057	0.005	0
8	0.000	0.000	0.001	0.004	0.007	0.019	0.046	0.163	0.854	0.130	0
9	0.000	0.000	0.000	0.000	0.001	0.001	0.005	0.019	0.061	0.625	0
10	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.008	0.239	1

NB: Natural history transition matrix is from RSS and based on information from British Columbia multiple sclerosis database

Model inputs: Transition probabilities by EDSS state
Onset of MS above the median age

EDSS state	0	1	2	3	4	5	6	7	8	9	10
0	0.695	0.058	0.016	0.006	0.002	0.001	0.000	0.000	0.000	0.000	0
1	0.203	0.695	0.121	0.050	0.022	0.005	0.001	0.000	0.000	0.000	0
2	0.073	0.158	0.608	0.120	0.067	0.029	0.004	0.001	0.000	0.000	0
3	0.022	0.061	0.168	0.544	0.115	0.059	0.025	0.002	0.000	0.000	0
4	0.004	0.016	0.045	0.091	0.489	0.087	0.031	0.007	0.001	0.000	0
5	0.001	0.005	0.019	0.058	0.104	0.487	0.041	0.004	0.001	0.000	0
6	0.002	0.006	0.022	0.117	0.168	0.273	0.741	0.117	0.019	0.001	0
7	0.000	0.001	0.002	0.010	0.026	0.039	0.109	0.693	0.055	0.004	0
8	0.000	0.000	0.001	0.004	0.007	0.019	0.044	0.161	0.896	0.133	0
9	0.000	0.000	0.000	0.000	0.001	0.001	0.004	0.016	0.021	0.623	0
10	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.003	0.239	1

EDSS STATE

NB: Natural history transition matrix is from RSS and based on information from British Columbia multiple sclerosis database

Model inputs: Relapse frequency

EDSS	Relapse frequency		Relapse frequency (%)	
	RRMS	SPMS	% RRMS	% SPMS
0	0.890	0.000	1.000	0.000
1	0.789	0.000	0.861	0.139
2	0.648	0.605	0.861	0.139
3	0.616	0.515	0.806	0.194
4	0.553	0.487	0.545	0.455
5	0.525	0.423	0.343	0.657
6	0.515	0.360	0.270	0.730
7	0.448	0.303	0.053	0.947
8	0.367	0.251	0.000	1.000
9	0.296	0.217	0.000	1.000
10	0.000	0.000	0.000	0.000

NB: Base case values obtained from the RSS model

Model inputs: Treatment effect

Disability progression (HR 95% CI)		Source
RSS model	0.791 (0.771, 0.812)	Base case value obtained from RSS model, and confidence intervals obtained from DH
Assessment group model	0.696 (0.553, 0.875)	Derived from assessment group analysis
Annualised relapse rate (RR 95%CI)		
RSS model	0.720 (0.526, 0.762)	Base case value obtained from RSS model, and confidence intervals derived from assessment group analysis
Assessment group model	0.649 (0.557, 0.757)	Derived from assessment group analysis

HR: hazard ratio; RR: Rate ratio; 95% CI: 95% confidence interval

Scenario analysis: treatment dominance

- Plegridy (pegylated IFN β-1a) dominates in several scenario analyses: it has the highest mean QALYs
- These scenario analyses use individual estimates of effectiveness
- Plegridy was not in the RSS and effectiveness estimates are from one short trial (ADVANCE, 2014)
- Copaxone (glatiramer acetate) dominates in several scenario analyses: it has the lowest mean costs
- These scenario analyses use pooled estimates of effectiveness and individual estimates of costs (results in spare slides)

⊙ *Does committee prefer pooled or individual treatment effects?*

⊙ *Would committee make a positive recommendation for only some of the drugs under appraisal?*

Treatment waning effect

- Assessment group modelled treatment waning effect in scenario analysis
- 50% reduction to the effect of treatments on disease progression after year 10 of the projection
- This follows RSS approach to uncertainty of a 50-year time horizon
- This is in line with precedents from other NICE appraisals where long-term effects have to be extrapolated from shorter-term data
- Previous committees (alemtuzumab, dimethyl fumarate) preferred to include waning effect, typically reduced treatment effect by 25% after year 2 and 50% after year 5

⊙ *Does committee think waning effect should be included, and if so is it content with AG's scenario analysis?*

Disability progression: 3 months or 6 months

Previous committees preferred 6 months

Assessment group model uses 3 months in its base case

- TTP3 was preferred for modelling by the assessment group because the quality and quantity of evidence in the network for TTP6 was considerably inferior to the network for TTP3

Alemtuzumab TA312

- Heard from experts:
  - Relapse recovery can take a year, typically 3 or 4 months
  - 6 months more appropriate outcome than 3 months
- Committee preferred to use 6 months in mixed treatment comparison (and hence model)

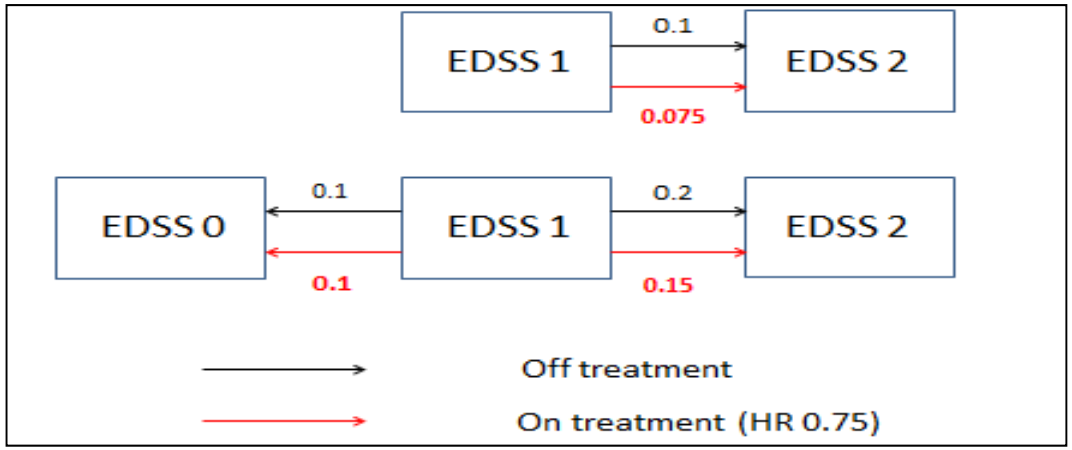
Dimethyl fumarate TA320

- Committee preferred 6 months for clinical effectiveness, but accepted 3 months for modelling
- ERG: although 6 months more closely associated with permanent progression, 3 months in model reasonable because patients could improve to lower EDSS states

⊙ *Does committee prefer to model disability progression sustained for 3 or 6 months?*

Individual drug treatment effects

- For scenario analyses using individual drug treatment effects, the AG has used relative hazard rates for disease progression derived from RCT data as a direct input to the RSS model
- Department of Health argue that this is invalid as the model assumes that backward transitions (disease regression) is unaffected by treatment
- It argues that this leads to an exaggerated effect of DMTs in slowing disease progression
- In the below example, while the off treatment net probability of progression is the same in each pathway (0.1), the on treatment probability of progression is less in the second pathway as backward transitions remain unaffected



⊙ *Has the assessment group overestimated the effectiveness of DMTs?*

Carer disutilities

- Assessment group questioned whether the inclusion of carer disutilities was consistent with NICE reference case
- Carer disutilities were therefore excluded from the base case
- Carer disutilities from RSS model (below) were used in scenario analyses
- The results suggested that the cost-effectiveness of the interventions is not sensitive to the inclusion/exclusion of carer disutilities

EDSS	Carer's disutility	EDSS	Carer's disutility
0	-0.002	**6**	-0.167
1	-0.002	**7**	-0.063
2	-0.002	**8**	-0.095
3	-0.002	**9**	-0.095
4	-0.045	**10**	0
5	-0.142		

⊙ *Does committee think carer disutilities should be accounted for in the economic model?*

DH cost-effectiveness estimates using the RSS model and year 10 data

DMT	Without "waning"			With "waning"		
	Net cost	Net QALYs	ICER	Net cost	Net QALYs	ICER
All RSS DMTs	£31,684	1.047	£30,262	£35,695	0.900	£39,648
IFN β-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1b 250 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a. NHS list prices; "implied hazard ratios" and discontinuation rates from the year 10 RSS data; relative relapse rates from the AG; including carer disutilities; SMR for general mortality = 1 as in the AG's base case

b. Weighted average of all DMTs in the RSS, using the relative proportions in the RSS cohort as the weights

c. Weighted average of estimates for Rebif 22 and Rebif 44, using the relative proportions in the RSS cohort as the weights

Assessment group cost-effectiveness estimates using the RSS model and year 10 data

DMT	Without "waning"			With "waning"		
	Net cost	Net QALYs	ICER	Net cost	Net QALYs	ICER
All RSS DMTs	£25,600	1.046	£24,500	£29,700	0.899	£33,100
IFN β-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1b 250 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a. List prices; companies' "implied hazard ratios"; 5% discontinuation rates relative relapse rates from the AG; including carer disutilities; SMR for general mortality = 1 as in the AG's base case

b. Weighted average of estimates for Rebif 22 and Rebif 44

Cost-effectiveness results
Assessment group base case using pooled RSS estimates

Strategy	Mean cost	Incremental costs	Mean QALYs	Incremental QALYs	ICER
Best supportive care	£362,100	-	8.664	-	-
Disease modifying treatments	£387,800	£25,600	9.607	0.943	£27,200
Probabilistic Sensitivity Analysis					
Best supportive care	£363,900	-	8.89	-	-
Disease modifying treatments	£389,300	£25,400	9.80	0.910	£27,900
RSS Original Analysis					
Disease modifying treatments	-	£25,600	-	1.013	£25,300

Assessment Group modifications to RSS base case:

- Exclusion of carers' disutilities
- Changes to mortality assumptions to avoid double counting

DH cost-effectiveness estimates using Assessment Group modifications to RSS model

DMT	Without "waning"			With "waning"		
	Net cost	Net QALYs	ICER	Net cost	Net QALYs	ICER
All RSS DMTs	31,838	0.943	33,748	35,845	0.812	44,151
IFN β-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1b 250 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Changes from DH base case:
(a) carer utilities are excluded
(b) the product-specific discontinuation rates estimated by the Assessment Group are used in place of the common assumption of a 5% discontinuation rate derived from the RSS year 8 data.

Differences in ICERs from AG basecase explained by the average price of DMTs in aggregate. DH used £8,000 while AG used £7,300. DH found a comparable ICER when using the lower average price

Cost-effectiveness scenario analysis
Pooled Assessment Group Review Estimates

Strategy	Mean cost	Incremental costs	Mean QALYs	Incremental QALYs	ICER
Best supportive care	£362,100	-	8.664	-	-
Disease modifying treatments	£376,900	£14,800	10.486	1.822	£8100
Probabilistic Sensitivity Analysis					
Best supportive care	£363,400	-	8.87	-	-
Disease modifying treatments	£373,500	£10,100	10.26	1.39	£7300

Cost-effectiveness results
Assessment Group clinical review estimates – individual drug effectiveness, treatment-waning and carer disutilities

Strategy	Mean cost	Incremental costs	Mean QALYs	Incremental QALYs	ICER
Best supportive care	£362,100	-	7.148	-	-
Glatiramer acetate 20 mg	£388,600	£26,500	8.371	1.223	Extendedly dominated
pegIFN β-1a 125 mcg	£395,500	£33,400	9.354	2.206	£15,100
IFN β-1b 250 mcg	£400,300	£4800	8.292	-1.062	Dominated
IFN β-1a 4mcg	£406,000	£10,500	9.107	-0.247	Dominated
IFN β-1a 30mcg	£415,900	£20,400	8.626	-0.728	Dominated

NB: TTP3 used rather than TTP6

Department of Health Sensitivity Analyses

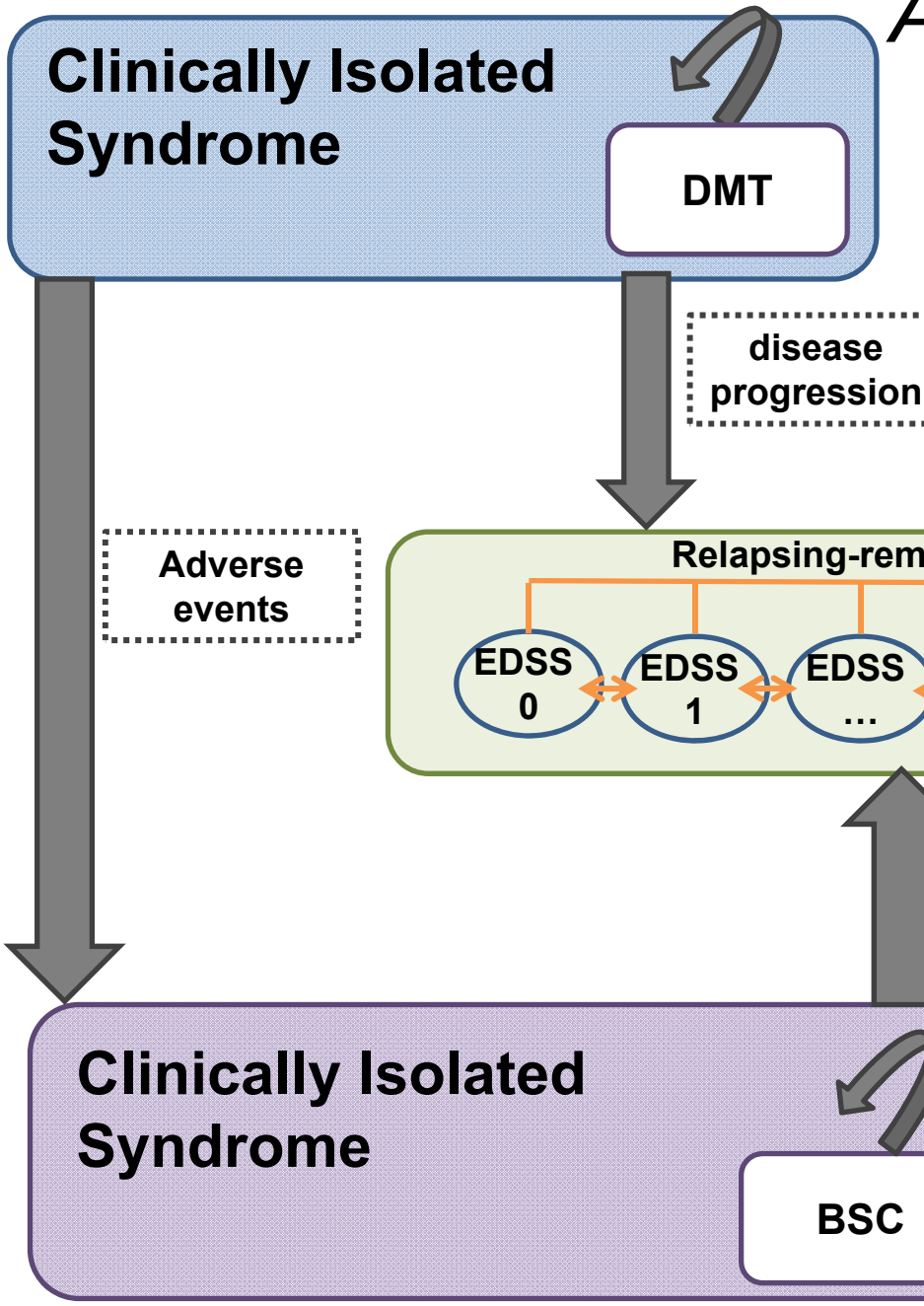
DMT	Without "waning"			With "waning"		
	Net cost	Net QALYs	ICER	Net cost	Net QALYs	ICER
Base run	£31,684	1.047	£30,262	£35,695	0.900	£39,648
C1a	£29,998	1.113	£26,956	£34,303	0.955	£35,921
C1b	£28,197	1.183	£23,830	£32,821	1.013	£32,392
C2	£31,894	1.039	£30,702	£35,868	0.893	£40,144
C3a	£29,645	1.026	£28,902	£34,327	0.875	£39,239
C3b	£32,528	1.042	£31,202	£36,345	0.898	£40,464
C4	£23,095	1.309	£17,643	£28,334	1.120	£25,308

C1a: excluding data after patients have switched to a non-scheme DMT.
C1b: excluding data after patients have switched to any other DMT.
C2: missing data in the RSS imputed using the multilevel model to project forward from the available data for each patient.
C3a: assumes that DMTs reduce the rate of backward transitions in the same proportion as for forward transitions [nb in the base run it is assumed that DMTs have no effect on the rate of backward transitions]
C3b: assumes that DMTs increase the rate of backward transitions in inverse proportion to the effect on forward transitions.
C4: using transition matrices augmented to adjust for missing data in the BCMS dataset.

CIS: cost-effectiveness modelling

Assessment Group Model

Clinically isolated syndrome



Assumptions

1. *Starting population 30 years old with clinically isolated syndrome*
2. *No residual DMT benefit after progressing to RRMS*
3. *RRMS pathway same as in RSS model*
4. *RRMS treatment discontinuation independent of CIS treatment discontinuation*

DEATH
(from any state)

EDSS 10

Summary of assessment group CIS model inputs

Parameters	Assessment group's source of evidence
Baseline characteristics	• People aged 30 years and with CIS
Best supportive care: transitions from CIS to RRMS	• Kerbrat et al., 2015
Treatment with DMTs: transitions from CIS to RRMS	• Assessment group clinical review
Treatment effect intervention	• Survival extrapolation based on Kerbrat et al (2105)
Utility data	• MS Trust survey 2002 and 2005 • Tappenden et al (2001)
Costs	• Health state costs: Curtis and Burns (2015), NHS reference costs 2014/15 • Drug administration costs: Curtis and Burns (2015) • Drug costs BNF 2015
Rate of stopping treatment	• By individual drug: Jacobs et al (2000), Mikos et al (2008), Kappos et al (2006), Comi et al (2009)

CIS Model Inputs: Resource use and costs

Parameter	Cost (£, 2015)	Reference
Drug costs		
IFN β-1a 30 mcg	8,502	British National Formulary (BNF), 2015
IFN β-1a 44 mcg	10,572	
IFN β-1b 250 mcg	7,264	
Glatiramer acetate	6,704	
Monitoring costs		
IFN β-1a 30 mcg	553.20	Estimates on resource use from clinical expert and unit costs from BNF 2015, NHS reference costs 2014/15 and Curtis and Burns 2015
IFN β-1a 44 mcg	560.33	
IFN β-1b 250 mcg	553.20	
Glatiramer acetate	553.20	
Cost of subsequent monitoring	323.77	
Other costs		
Drug administration	225.00	Assumption on resource use information and unit costs from Curtis and Burns 2015 and NHS reference costs 2014/15
CIS no treatment	350.49	

CIS Model Inputs: Transition Probabilities

Treatment	Base-case value	HR (95% CI)	Reference
Best supportive care	Weibull (λ = 0.0906; γ = 0.6768)	-	• Assessment group reconstructed individual patient data from Kerbrat et al., 2015 • Found that Weibull model was a good parametric fit • Applied hazard ratios derived from the clinical effectiveness review
IFN β-1a 30 mcg		0.516 (0.389, 0.684)	
IFN β-1a 44 mcg		0.480 (0.314, 0.738)	
IFN β-1b 250 mcg		0.500 (0.36, 0.699)	
Glatiramer acetate		0.549 (0.397, 0.762)	

Model Inputs
Utilities

Parameter	Cost (£, 2015)	
Health state utility values		
CIS	0.6218	Assumption based on MS Trust survey 2002 and 2005
Disutility associated with AEs		
IFN β-1a 30 mcg IM once a week (Avonex)	-0.02	Tappenden et al, 2001
IFN β-1a 44 mcg SC three times per week (Rebif)	-0.02	
IFN β-1b 250 mcg SC every other day (Betaferon/Extavia)	-0.02	
Glatiramer acetate 20 mg SC daily (Copaxone)	-0.02	

Merck CIS model

- Same model structure as for DMTs, with an additional 5 on treatments and 5 off treatment health states defined by EDSS score
- Patients' baseline EDSS is as in REFLEX
- Conversion from CIS is as in REFLEX for delayed treatment, with relative risks for years one and two calculated from REFLEX
- No treatment effect is applied beyond year two, though patients are assumed to remain on treatment for up to 5 years with CIS
- Patients are assumed to remain in the starting EDSS during and upon conversion to MS
- **Results are confidential**

Summary of assessment group CIS model inputs

Parameters	Assessment group's source of evidence
Baseline characteristics	• People aged 30 years and with CIS
Best supportive care: transitions from CIS to RRMS	• Kerbrat et al., 2015
Treatment with DMTs: transitions from CIS to RRMS	• Assessment group clinical review
Treatment effect intervention	• Survival extrapolation based on Kerbrat et al (2105)
Utility data	• MS Trust survey 2002 and 2005 • Tappenden et al (2001)
Costs	• Health state costs: Curtis and Burns (2015), NHS reference costs 2014/15 • Drug administration costs: Curtis and Burns (2015) • Drug costs BNF 2015
Rate of stopping treatment	• By individual drug: Jacobs et al (2000), Mikos et al (2008), Kappos et al (2006), Comi et al (2009)

CIS: Assessment group's base case results

Strategy	Mean cost	Incremental costs	Mean QALYs	Incremental QALYs	ICER
BSC (CIS and RRMS)	£136,800	-	12.78	-	-
BSC for CIS and DMTs for RRMS	£150,700	£13900	13.16	0.38	Extendedly dominated
IFN β-1b 250 mcg	£196,400	£45,700	16.85	3.69	Extendedly dominated
Glatiramer acetate 20 mg	£213,700	£76,900	18.73	5.95	£12,900
IFN β-1a 30 mcg	£231,300	£17,900	18.57	-0.16	Dominated
IFN β-1a 44 mcg	£240,300	£26,900	17.61	-1.12	Dominated

Innovation and equalities considerations

- If care is provided only in a specialist centre, people who are unable to travel due to a disability may find it difficult to access treatment
- Healthcare Improvement Scotland: "*As most of patients are females, the concern with pregnancy is a fact that should be included in the analysis. We know that glatiramer acetate is the safest drug to be used in young females who want to become pregnant in the future*"

Key issues

- Are beta interferon and glatiramer acetate clinically effective for RRMS? Are all the technologies equally as effective?
- Which analyses reflect clinical practice (NMA or RSS?)
- Are the trial results for clinically isolated syndrome generalisable? glatiramer acetate clinical effective for CIS
- Does the committee prefer results including treatment waning effects and carer disutilities?
- Does the committee prefer the treatment effectiveness estimates from the risk sharing scheme or from the assessment group meta-analysis?
- Innovation
- Equalities
- PPRS

Spare slides

Assessment Group Analyses

Parameter	RSS	AG base case analysis	SA1
Time horizon	20-year in base run model And 50-year in base run with time-varying DMT effect	50-year in base run model	50-year in base run model And 50-year in base run with time-varying DMT effect
Annual discontinuation rate	5%	As in RSS	AG review (pooled results)
Annualised relapse rate	0.720	As in RSS	AG review (pooled results)
Disability progression	0.7913	As in RSS	AG review (pooled results)
Carers' disutilities	Included	Excluded	Excluded / Included
Drug acquisition costs	7300	As in RSS	As in RSS
SMR	2	1	1
Method for backward transitions	Method 2: no impact of DMTs on backward transitions	As in RSS	As in RSS

Assessment Group Analyses Continued

Parameter	SA2a	SA2b	SA3
Time horizon	50-year in base run model And 50-year in base run with time-varying DMT effect	50-year in base run model And 50-year in base run with time-varying DMT effect	50-year in base run model And 50-year in base run with time-varying DMT effect
Annual discontinuation rate	AG review for each DMT	AG review for each DMT	Company submission
Annualised relapse rate	AG review for each DMT	AG review for each DMT	Company submission
Disability progression	AG review for each DMT	AG review for each DMT	Company submission
Carers' disutilities	Excluded / Included	Excluded / Included	Excluded / Included
Drug acquisition costs	List prices / Price discounts+/- Infrastructural contributions	List prices	List prices
SMR	1	1	1
Method for backward transitions	As in RSS	As in RSS	As in RSS

Assessment Group Analyses Continued

Parameter	SA4	SA5	SA6
Time horizon	20, then 30-year in base run model Same as above with time-varying DMT effect	50-year in base run model Same as above with time-varying DMT effect	50-year in base run model 50-year in base run with time-varying DMT effect
Annual discontinuation rate	AG clinical effectiveness review for each DMT	As in the RSS and varied by ±10% (base case and SA1)	As in RSS
Annualised relapse rate	AG review (pooled results)	AG review (pooled results) and varied by ±10% (base case and SA1)	Pooled treatment effect derived from AG clinical effectiveness review for each DMT
Disability progression	AG review (pooled results)	AG review (pooled results) and varied by ±10% (base case and SA1)	Pooled treatment effect derived from AG clinical effectiveness review for each DMT
Carers' disutilities	Excluded / Included	Excluded / Included	Excluded / Included
Drug acquisition costs	List prices	Using the drug acquisition costs in RSS and varied by ±10% (base case and SA1)	List prices / Price discounts+/- Infrastructural contributions
SMR	1	1	1
Method for backward transitions	As in RSS	As in RSS	As in RSS

AG Cost-effectiveness results
Pooled Assessment Group estimates with carer disutilities and time-varying effects

Strategy	Mean cost	Incremental costs	Mean QALYs	Incremental QALYs	ICER
Best supportive care	£362,100	-	7.148	-	-
Glatiramer acetate 20 mg	£380,400	£18,300	8.771	1.623	£11,300
IFN β-1b 250 mcg	£387,000	£6600	8.771	0.000	Dominated
IFN β-1a 30mcg	£401,600	£21,200	8.771	0.000	Dominated
IFN β-1a 44mcg SC	£415,800	£35,400	8.771	0.000	Dominated

Cost-effectiveness results
Assessment Group estimates – individual drug effectiveness

Strategy	Mean cost	Incremental costs	Mean QALYs	Incremental QALYs	ICER
Best supportive care	£362,100	-	8.664	-	-
IFN β-1a 125mcg	£379,900	£17,800	11.223	2.559	£7000
Glatiramer acetate 20mg	£381,400	£1500	10.012	-1.211	Dominated
IFN β-1b 250mcg	£393,400	£13,500	9.934	-1.289	Dominated
INF β-1a 44mcg SC	£404,800	£24,900	10.867	-0.356	Dominated
IFNβ-1a 30mcg IM	£406,400	£26,500	10.348	-0.875	Dominated

NB: TTP3 used rather than TTP6

AG Cost-effectiveness results
Individual treatment effects with carer disutilities

Strategy	Mean cost	Incremental costs	Mean QALYs	Incremental QALYs	ICER
Best supportive care	£362,100	-	7.148	-	-
IFN β-1a 125 mcg	£366,300	£4200	8.566	1.418	£3000
Glatiramer acetate 20 mg	£374,600	£8300	8.432	-0.134	Dominated
IFN β-1a 30mcg	£387,600	£21,300	8.149	-0.417	Dominated
IFN β-1a 44mcg	£405,200	£38,900	8.318	-0.248	Dominated

AG Cost-effectiveness results
Individual time-varying treatment effects

Strategy	Mean cost	Incremental costs	Mean QALYs	Incremental QALYs	ICER
Best supportive care	£362,100	-	8.664	-	-
IFN β-1a 125 mcg	£369,900	£7800	9.818	1.154	£6800
Glatiramer acetate 20 mg	£379,900	£10,000	9.654	-0.164	Dominated
IFN β-1a 30mcg	£390,600	£20,700	9.467	-0.351	Dominated
IFN β-1a 44mcg	£409,500	£39,600	9.570	-0.248	Dominated

AG Cost-effectiveness results
Individual time-varying treatment effects, carer disutilities and 20-year time horizon

Strategy	Mean cost	Incremental costs	Mean QALYs	Incremental QALYs	ICER
Best supportive care	£196,900	-	5.710	-	-
Glatiramer acetate 20 mg	£223,000	£26,100	6.552	0.842	Extendedly dominated
IFN β-1a 125 mcg	£229,800	£32,900	7.150	1.44	£22,800
IFN β-1b 250 mcg	£232,800	£3000	6.492	-0.658	Dominated
IFN β-1a 44mcg	£239,700	£9900	7.030	-0.12	Dominated
IFN β-1a 30mcg	£245,700	£15,900	6.689	-0.461	Dominated

AG Cost-effectiveness results
Individual time-varying treatment effects, carer disutilities and 30-year time horizon

Strategy	Mean cost	Incremental costs	Mean QALYs	Incremental QALYs	ICER
Best supportive care	279,400	-	6.540	-	-
Glatiramer acetate 20 mg	304,500	25,100	7.614	1.074	Extendedly dominated
IFN β-1a 125 mcg	310,400	31,000	8.425	1.885	16,400
IFN β-1b 250 mcg	315,600	5200	7.541	-0.884	Dominated
IFN β-1a 44mcg	320,900	10,500	8.242	-0.183	Dominated
IFN β-1a 30mcg	329,900	19,500	7.813	-0.612	Dominated

AG Cost-effectiveness results
Company estimates of effectiveness

Strategy	Mean cost	Incremental costs	Mean QALYs	Incremental QALYs	ICER
Best supportive care	£362,100	-	8.664	-	-
IFN β-1a 125mcg	£366,300	£4200	9.931	1.267	£3300
Glatiramer acetate 40mg	£374,600	£8300	9.821	-0.11	Dominated
IFNβ-1a 30mcg IM	£387,600	£21,300	9.563	-0.368	Dominated
INF β-1a 44mcg SC	£405,200	£38,900	9.719	-0.212	Dominated

Cost-effectiveness results: Biogen base case

Treatment	Total costs	Total life years	Total QALYs	Incr. costs	Incr. QALYs	ICER vs BSC
BSC	£177,562	20.543	8.831	£0	0.000	N/A
SC pegIFNβ-1a 125 mcg	**£202,721**	**20.658**	**9.642**	**£25,159**	**0.810**	**£31,044**
SC IFNβ-1a 44 mcg	£209,954	20.640	9.516	£7,233	-0.126	£47,314
GA 20 mg	£211,016	20.565	9.007	£8,295	-0.635	£190,657
GA 40 mg	£211,105	20.565	9.001	£8,385	-0.640	£197,167
IM IFNβ-1a 30 mcg	**£212,298**	**20.635**	**9.381**	**£9,577**	**-0.260**	**£63,163**
IFNβ-1b 250 mcg	£220,211	20.547	8.807	£17,490	-0.835	Dominated

NB: Biogen does not offer a discount and therefore results can be shown in part 1. Merck and Teva both offer confidential discounts and therefore their analysis is in part 2

CIS Sensitivity analysis: 20-year time horizon

Strategy	Mean cost	Incremental costs	Mean QALYs	Incremental QALYs	ICER
BSC (CIS and RRMS)	£155,100	-	10.33	-	-
BSC for CIS and DMTs for RRMS	£166,400	£11,300	10.73	0.40	Extendedly dominated
IFN β-1b 250 mcg	£181,600	£26,500	11.99	1.66	£16,000
Glatiramer acetate 20 mg	£190,400	£8800	12.46	0.47	£18,700
IFN β-1a 30 mcg	£204,100	£13,900	12.39	-0.07	Dominated
IFN β-1a 44 mcg	£215,000	£24,800	12.15	-0.31	Dominated

CIS Sensitivity analysis: 5% treatment discontinuation

Strategy	Mean cost	Incremental costs	Mean QALYs	Incremental QALYs	ICER
BSC (CIS and RRMS)	£136,800	-	12.78	-	
BSC for CIS and DMTs for RRMS	£150,700	£13,900	13.16	0.38	Extendedly dominated
IFN β-1b 250 mcg	£188,700	£51,900	16.22	3.44	£15,100
Glatiramer acetate 20 mg	£191,100	£2400	16.36	0.14	£17,100
IFN β-1a 30 mcg	£204,000	£12,900	16.31	-0.05	Dominated
IFN β-1a 44 mcg	£222,200	£31,100	16.41	0.05	£622,000

CIS Sensitivity analysis: 30-year time horizon

Strategy	Mean cost	Incremental costs	Mean QALYs	Incremental QALYs	ICER
BSC (CIS and RRMS)	£173,100	-	12.02	-	-
BSC for CIS and DMTs for RRMS	£185,600	£12,500	12.46	0.44	Extendedly dominated
IFN β-1b 250 mcg	£212,000	£38,900	14.89	2.87	£13,500
Glatiramer acetate 20 mg	£225,800	£13,800	15.88	0.99	£13,900
IFN β-1a 30 mcg	£241,200	£15,700	15.78	-0.1	Dominated
IFN β-1a 44 mcg	£251,000	£25,500	15.28	-0.6	Dominated

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE
Multiple Technology Appraisal

Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32)

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of beta interferon and glatiramer acetate within their marketing authorisation for treating multiple sclerosis.

Background

Multiple sclerosis (MS) is a chronic, neurodegenerative disorder which affects the brain, optic nerves, and spinal cord. It often results in progressive neurological impairment and severe disability. Approximately 100,000 people in the UK have MS, and about 2500 people are newly diagnosed each year.

Relapsing-remitting MS (RRMS) is one clinical form of MS which affects approximately 80% of people at time of diagnosis. It is characterised by periods of remission followed by relapses (which may or may not result in residual disability). Most people with RRMS will develop secondary progressive MS (SPMS). Around 65% of people with RRMS develop SPMS within 15 years of diagnosis. SPMS is characterised by more persistent or gradually increasing disability. Some people with SPMS may still experience relapses. MS has an unpredictable course with variable severity and progression. Symptoms can include pain, disturbance to muscle tone including weakness or spasticity, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment.

There is currently no cure for MS. Current pharmacological management of MS includes disease-modifying agents to reduce the frequency and severity of relapses and the rate of disease progression. These include beta interferon and glatiramer acetate which are not currently recommended by NICE (technology appraisal guidance 32), but are available in the NHS through a risk-sharing scheme. NICE has recommended dimethyl fumerate, alemtuzumab and teriflunomide as treatment options for RRMS (Technology appraisal guidance 320,312 and 303 respectively). For people with rapidly-evolving severe RRMS, natalizumab is recommended as a treatment option (NICE technology appraisal guidance 127). NICE has recommended fingolimod as an option for the treatment of highly active RRMS in adults who have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon (NICE technology appraisal guidance 254).

At the time of technology appraisal guidance 32, beta interferon and glatiramer acetate were not considered to be cost effective. However, it was

recognised that the data on the long term outcomes of beta interferon and glatiramer acetate were limited. It was agreed by the Department of Health that beta interferon and glatiramer acetate would be made available to patients in the NHS if they entered a risk sharing scheme. The risk sharing scheme required an immediate price reduction (for 3 of the 4 products) and a contribution from the companies to NHS infrastructure costs. In addition, the long term clinical outcomes of patients receiving beta interferon and glatiramer acetate were to be recorded in a registry and the companies making these technologies were to make further price reductions to the NHS if cost effectiveness criteria were not met.

The companies included in the risk sharing scheme were Biogen Idec (Interferon beta 1a, Avonex), Merck (Interferon beta 1a, Rebif), Bayer (Interferon 1b, Betaferon) and Teva/Sanofi (Glatiramer acetate, Copaxone). People who were eligible to enter the risk sharing scheme were people with relapsing remitting MS and people with secondary progressive MS in whom relapses were the dominant feature, who meet the criteria laid down by the Association of British Neurologists in 2001. The risk sharing scheme was designed to run for 10 years and it is now due to end in 2016. The final data from this scheme will be considered in the appraisal.

In this appraisal NICE will appraise beta interferon and glatiramer acetate at their current NHS prices, and using additional data on long-term outcomes from the risk sharing scheme, to determine whether these technologies are now cost effective. To do so, NICE has determined that it needs to appraise these technologies within the context of the original appraisal (Technology Appraisal 32). That is, beta interferon and glatiramer acetate should be compared with best supportive care.

Since Technology Appraisal 32 was published another interferon 1b (Extavia, Novartis), a pegylated interferon beta 1a (Plegridy, Biogen Idec) and a new formulation of glatiramer acetate (Copaxone, Teva pharmaceuticals) have been granted marketing authorisations. These technologies were not included in the risk sharing scheme because they were not appraised in Technology Appraisal 32. It has been determined by NICE that it is relevant to include these technologies in this appraisal so that guidance can be issued for all beta interferons and formulations of glatiramer acetate currently licensed for MS in the UK. Further active treatments that have been licensed and recommended by NICE (including teriflunomide, fingolimod, natalizumab, alemtuzumab and dimethyl fumerate) will not be considered in this appraisal.

Some of the technologies in Technology Appraisal 32 are now also indicated for people with clinically isolated syndrome at high risk of developing clinically definite multiple sclerosis. The population with clinically isolated syndrome will be considered in addition to the population currently covered by the risk sharing scheme in this appraisal.

The technologies

Interferon beta 1 a (Avonex, Biogen Idec Ltd) is administered by intramuscular injection. It is indicated for:

- people diagnosed with relapsing multiple sclerosis. In clinical trials, this was characterised by 2 or more acute exacerbations (relapses) in the previous 3 years without evidence of continuous progression between relapses.

- people with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis.

Interferon beta 1a (Rebif, Merck) is administered by subcutaneous injection. It is indicated for:

- patients with a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis

- the treatment of relapsing MS. In clinical trials this was characterised by 2 or more acute exacerbations in the previous 2 years

Peginterferon beta 1a (Plegridy, Biogen Idec) is a pegylated interferon beta 1a. It is administered subcutaneously. It is indicated;

- in adult patients for the treatment of relapsing remitting multiple sclerosis.

Interferon beta 1b (Betaferon, Bayer) is administered by subcutaneous injection. It is indicated for:

- patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis.

- Patients with relapsing-remitting multiple sclerosis with 2 or more relapses within the last 2 years

- Patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.

Interferon beta 1b (Extavia, Novartis) is administered subcutaneously. It is indicated for:

- Patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis

- Patients with relapsing remitting multiple sclerosis and 2 or more relapses within the last 2 years

- Patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses

Glatiramer acetate (Copaxone, Teva Pharmaceuticals) is administered subcutaneously. It is indicated for:

- Patients who have experienced a first clinical episode and are determined to be at high risk of developing clinically definite multiple sclerosis

- Ambulatory patients (i.e. who can walk unaided) with relapsing, remitting multiple sclerosis characterised by at least 2 attacks of neurological dysfunction over the preceding 2-year period

Interventions	• Interferon beta 1a • Peginterferon beta 1a • Interferon beta 1 b • Glatiramer acetate
Population	• People with relapsing remitting multiple sclerosis (including people with relapsing remitting multiple sclerosis and people with secondary progressive multiple sclerosis with active disease, evidenced by relapses) • People with clinically isolated syndrome, that is, a single demyelinating event, who are considered at high risk of developing multiple sclerosis
Comparators	For both populations the comparators are: • Best supportive care without disease modifying treatment • If appropriate, the beta interferons and glatiramer acetate will be compared with each other

Outcomes	• relapse rate • severity of relapse • disability (for example, expanded disability status scale [EDSS]) • symptoms of multiple sclerosis such as fatigue, cognition and visual disturbance • freedom from disease activity • presence of neutralising antibodies • mortality • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The economic model for relapsing remitting MS will be based on the model used in the risk sharing scheme, including any changes that have been made to the model since 2002. The model parameters and inputs will be updated where necessary to reflect current costs, the NICE reference case and current practice, and any new data from the risk sharing scheme. If appropriate, any continuing contributions made by the companies who manufacturer technologies for multiple sclerosis to the infrastructure for multiple sclerosis management, should be taken into account in determining cost effectiveness.

Other considerations	It is recognised that best supportive care without a disease modifying treatment is not current established clinical practice for treating relapsing remitting multiple sclerosis. Best supportive care was the comparator for beta interferon and glatiramer acetate in TA32 and therefore is included as the comparator for this appraisal. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Dimethyl fumarate for treating relapsing-remitting multiple sclerosis' (2014). NICE Technology Appraisal 320. Review date to be confirmed 'Alemtuzumab for treating relapsing remitting multiple sclerosis' (2014). NICE Technology Appraisal 312. Review date to be confirmed 'Teriflunomide for treating relapsing-remitting multiple sclerosis' (2014). NICE Technology Appraisal 303. Review date to be confirmed 'Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis (2012). NICE Technology Appraisal 254. Review date to be confirmed 'Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis' (2007). NICE Technology Appraisal 127. Review date to be confirmed 'Beta interferon and glatiramer acetate for the treatment of multiple sclerosis' (2002) NICE Technology Appraisal 32. Related Guidelines: 'Multiple sclerosis' (2014). NICE guideline 186 Review date December 2016. Related NICE Pathways: Multiple Sclerosis. NICE pathway http://pathways.nice.org.uk/
Related National Policy	NHS England. Manual for prescribed specialised services for 2013/14 chapter 11 adult specialist

	neurosciences services. http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf NHS England. Clinical Commissioning Policy. Disease modifying therapies for patients with multiple sclerosis, May 2014 https://www.england.nhs.uk/wp-content/uploads/2013/10/d04-p-b.pdf Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. Domains 1-5 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf

APPENDIX C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Beta interferon and glatiramer acetate for multiple sclerosis (review of TA32) [ID809]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Manufacturers/sponsors • Bayer (interferon beta 1b) • Biogen Idec (interferon beta 1a, peginterferon beta 1a) • Merck Serono (interferon beta 1a) • Novartis (interferon beta 1b) • Teva Pharmaceuticals (glatiramer acetate) Patient/carer groups • Afiya Trust • Black Health Agency • Brain and Spine Foundation • Disability Rights UK • Multiple Sclerosis National Therapy Centres • MS UK • Multiple Sclerosis Society • Multiple Sclerosis Trust • Muslim Council of Britain • Neurological Alliance • Neurosupport • South Asian Health Foundation • Specialised Healthcare Alliance • Sue Ryder Professional groups • Association of British Neurologists • British Geriatrics Society • British Neuropathological Society • British Society of Rehabilitation Medicine • Chartered Society of Physiotherapy • Institute of Neurology • Primary Care Neurology Society • Royal College of General Practitioners • Royal College of Nursing	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • Multiple Sclerosis Society Wales • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium • Wales Neurological Alliance Comparator manufacturers* * included on the matrix because NICE has recommended their products in related technology appraisals. It is not intended that these products will be comparators in the current appraisal. • Biogen Idec (dimethyl fumarate, natalizumab) • Genzyme (alemtuzumab, teriflunomide) • Novartis (fingolimod) Relevant research groups • Brain Research Trust • British Neurological Research Trust • Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System • MRC Clinical Trials Unit

• Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • Therapists in MS • United Kingdom Clinical Pharmacy Association • United Kingdom Multiple Sclerosis Specialist Nurse Association <u>Others</u> • Department of Health • NHS England • NHS Ipswich and East Suffolk CCG • NHS Nottingham City CCG • Welsh Government	• National Institute for Health Research • Research Institute for the Care of Older People <u>Associated Guideline Groups</u> • National Clinical Guidelines Centre <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the manufacturer(s) or sponsor(s) of the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The manufacturer/sponsor of the technology are invited to prepare a submission dossier, can respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).
All non-manufacturer/sponsor consultees are invited to prepare a submission dossier respond to consultations on the draft scope, the Assessment Report and the Appraisal Consultation Document. They can nominate clinical specialists and/or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but are not asked to prepare a submission dossier. Commentators are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: manufacturers of comparator technologies; Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.
All non-manufacturers/sponsors commentator organisations can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Evidence Review group

An independent academic group (commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist in the appraisal) prepares an Assessment Report on the health technology (a review of the clinical and cost effectiveness of the technology(ies)) based on a systematic review of the manufacturer/sponsor and non-manufacturer/sponsor submission dossier to the Institute.

NICE National Institute for Health and Care Excellence

NICE guidance

Beta interferon and glatiramer acetate for the treatment of multiple sclerosis

Technology appraisal guidance
Published: 23 January 2002
nice.org.uk/guidance/ta32

Contents

1 Guidance

1.1 On the balance of their clinical and cost effectiveness neither beta interferon nor glatiramer acetate is recommended for the treatment of multiple sclerosis (MS) in the NHS in England and Wales.

1.2 It is likely that patients currently receiving beta interferon or glatiramer acetate for MS, whether as routine therapy or part of a clinical trial, could suffer loss of well being if their treatment is discontinued at a time they did not anticipate. Because of this, all NHS patients who are on therapy at the date of publication of this guidance should have the option to continue treatment until they and their consultant consider it is appropriate to stop, having regard to the criteria established for withdrawal from treatment in the Guidelines of the Association of British Neurologists published in January 2001. This also applies to all participating patients at the conclusion of a clinical trial (irrespective as to whether they had received placebo or active drug) and women whose therapy has been interrupted by pregnancy.

1.3 The Department of Health and the National Assembly for Wales are invited to consider the strategy outlined in Section 7.1 with a view to acquiring any or all of the medicines appraised for this guidance in a manner that could be considered to be cost effective.

2 Clinical need and practice

2.1 MS is a disabling neurological disease. It is estimated that in England and Wales MS affects some 63,000 people. MS usually begins in individuals aged between 20 and 40 years, and occurs in about twice as many women as men. It is characterised by repeated episodes of inflammation of the nervous tissue in the brain and spinal cord, resulting in the removal of the insulating myelin sheath covering the nerves. Multiple areas of scar tissue (sclerosis) form along the nerve fibres, slowing or blocking the transmission of signals to and from the brain and spinal cord, so that functions such as movement and sensation may be lost.

2.2 There are several forms of MS. Some 80–90% of people start with relapsing remitting MS (RRMS). In this form of the disease, recurrent attacks of loss of neurological function, termed relapses, are separated by periods of complete or incomplete recovery, described as remissions. After about 10 years (without treatment), about half of people with MS begin a continuous downward progression, which may also include acute relapses. This form of MS is known as secondary progressive (SPMS). RRMS accounts for about 45% and SPMS for about 45 % of the total population with MS. In a third type of MS, primary progressive (accounting for about 10% of cases), the disease progresses inexorably from onset. Benign MS is a fourth and relatively rare condition.

2.3 Magnetic resonance imaging (MRI) shows that lesions develop in the brain and spinal cord tissues as the disease progresses. Development of MRI lesions may not initially correlate directly with the clinical manifestations of the disease as lesions often occur in 'silent' areas of the brain and spinal cord. However, lesions may precede the onset of overt symptoms of MS, and MRI data have been used as a surrogate marker of disease activity and/or progression.

2.4 The course of MS is unpredictable with variations in severity and progression rate. It tends to progress faster in men and people who are older at the time of onset.

2.5 The disease has an adverse and often highly debilitating impact on the quality of life of people with MS and their families. Relapses may require admission to hospital, and be associated with a level of disability and incapacity that disrupts working, family and social life. MS, even in its early stages, undermines patients'

confidence, restricts their activity and may limit their role in society in many ways including inability to continue employment or to take part in usual family activities. Weakness, chronic fatigue, unsteady gait, speech problems and incontinence can leave people with MS feeling isolated and depressed. Substantial burdens, including emotional and financial burdens, are imposed on primary/informal carers, who are often patients' partners. In the management of MS, emphasis is often placed on the problems of long-term disability. However, the emotional impact of relapses on patients and carers is also considerable.

2.6 The progression of MS is usually measured using the Expanded Disability Status Scale (EDSS). This scale is measured in half units from 0, which represents no disability, to 10, which denotes death; 7 denotes 'essentially restricted to wheelchair'. An important feature of the EDSS scale, however, is that it is non-linear, and small incremental changes reflect a much greater effect on patients' quality of life and dependency levels the higher they are on the EDSS scale. The full scale is set out in Appendix D.

3 The technologies

3.1 There are four general approaches to the treatment of MS, which may be undertaken separately or in combination:

- Management of symptoms and disability with speech, physio- and occupational therapy and pharmacological or other therapeutic agents;
- Management of the emotional and social consequences of relapses and disability;
- Treatment of acute relapses with corticosteroids;
- Disease-modifying treatment targeted at reducing the frequency and/or severity of relapses and/or slowing the course of the disease. The beta interferons and glatiramer acetate constitute the only options presently available in this category.

Beta interferons

3.2 There are three beta interferon products: Avonex (manufactured by Biogen) and Rebif (Serono) are interferon beta-1a products licensed only for the treatment of RRMS. Betaferon (Schering) is interferon beta-1b and is licensed for the treatment of both RRMS and SPMS .

3.3 The beta interferons work by reducing the inflammatory process that characterises MS. Such inflammation usually precedes an MS relapse. However, the precise mode of action of these disease-modifying agents on immunological mechanisms remains uncertain.

3.4 The beta interferons commonly cause temporary influenza-like adverse effects (in about 50% of patients), as well as injection site reactions and leucopenia. Less commonly, the use of the beta interferons is associated with symptoms of depression. In addition, these agents, by the nature of their chemical structure, have antigenic effects and therefore may induce the development of antibodies, high titres of which have been observed in some patients. Theoretically, these antibodies may produce allergic reactions or bind to the drug molecule neutralising its effects. The significance of these antibodies on the effectiveness of the beta interferons is uncertain, as such effects have not been reported in clinical practice.

3.5 Based on a survey of health authorities in England and Wales, undertaken in January 2000, an estimated 1,750 people are currently prescribed beta interferons, which equates to 2.8% of all MS patients, or 3.3% of those with RRMS or SPMS. These percentages vary between health authorities.

3.6 The current annual cost per patient of the beta interferons in the UK is £7,259 (Betaferon), £9,061 (Avonex) or £9,088/£12,068 (lower dose/higher dose Rebif).

Glatiramer acetate

3.7 Glatiramer acetate (Copaxone, TEVA/Aventis) is licensed for the treatment of RRMS.

3.8 Glatiramer acetate works by reducing the inflammation around nerves. Such inflammation usually precedes an MS relapse. Glatiramer is an acetate salt of polypeptides formed from the synthesis of four amino acids. It resembles myelin, the basic protein that is found in the sheath surrounding nerves. In structure, therefore, glatiramer is quite distinct from the beta interferons. Its exact mode of action, as with the beta interferons, is unknown, but it is thought also to inhibit antigen presentation to white blood cells and to induce antigen-specific suppressor T cells.

3.9 Glatiramer acetate can cause flushing, chest tightness, palpitations, anxiety and breathlessness, and also injection site reactions, but these effects are generally easily managed. In addition, by the nature of its chemical structure, glatiramer acetate has antigenic effects and therefore may induce the development of antibodies in patients. Theoretically these antibodies may produce allergic reactions or bind to the drug molecule neutralising its effects. The significance of these antibodies on the effectiveness of glatiramer is uncertain as such effects have not been reported in clinical practice.

3.10 The cost per patient of glatiramer acetate is £6,650 per year.

4 Evidence

Clinical effectiveness: beta interferons

4.1 Clinical trials have shown that all three interferon products reduce relapse frequency and severity in patients with RRMS and may also influence duration of relapse. The reduction in frequency amounts to about 30% on average, and is equivalent to approximately one relapse avoided every 2.5 years in people with RRMS. This reduction has been demonstrated for the first 2 years of therapy.

4.2 Disability progression is delayed by treatment, but the effects of treatment on disability in the long term, following cessation of therapy, cannot be predicted reliably on the basis of the short-term evidence from the clinical trials seen by the Committee.

4.3 The proposition that the beta interferons have a positive effect beyond 2 years is supported by open-label studies. These longer-term studies have assessed the effectiveness of beta interferon by comparing observed with expected levels of disease activity. For people who have taken the drug in studies for approximately 4 years, disease activity appears to be lower than might otherwise be expected from studies of the natural history of MS.

4.4 One of the interferon products (Betaferon) has also been shown to reduce relapse frequency and severity in SPMS. In a clinical trial in SPMS of another interferon product there was a difference from placebo in reduction of relapse frequency but this effect did not reach formal statistical significance.

Clinical effectiveness: glatiramer acetate

4.5 Clinical trials have shown that glatiramer acetate reduces relapse frequency in patients with RRMS. This reduction amounts to about 30% on average, which is equivalent to approximately one relapse avoided every 2.5 years. This reduction has been adequately demonstrated for the first 2 years of therapy.

4.6 Data from an open-label follow-up study of a small number of people (73) with RRMS showed that 75% of them were unchanged or improved in terms of accumulation of disability after 8 years using glatiramer acetate.

Clinical effectiveness: general

4.7 There is evidence of the value of MRI as a marker of disease activity in MS. The Committee interpreted the MRI findings from published clinical trials as supportive of its conclusions on the clinical effectiveness of these products in MS. In routine clinical practice in England and Wales, MRI scanning has not been used as a direct measure of the progress of MS or of the response to therapeutic intervention in preference to assessment of the clinical symptoms and signs of the disease.

4.8 The Committee considered in detail evidence taken directly from patients and two advocacy organisations (see Appendix B). The patient organisations and the patients who attended the Committee meeting spoke of the patients' experience of this distressing disease and of the impact of the beta interferons and glatiramer on relapses and disease progression. This dialogue provided important insight into the effect of relapses on patients' daily lives and the value that they place on the potential avoidance and reduction in severity of relapses with the use of these drugs, as well as into the more general effects of MS on quality of life and capacity to work. The Committee was also provided with recently published evidence for the effect of MS on cognitive function (for example, difficulties with memory and general alertness), which was in addition to the impact of relapses on quality of life. It was clear from the representations made to the Committee by these individuals and groups that they considered that these medicines had a very positive effect in some people with MS.

Cost effectiveness

4.9 During 2000 the Committee reviewed models of the cost effectiveness of the medicines submitted by each manufacturer and two models prepared by independent sources. All the models calculated cost-utilities – costs per-quality-adjusted life year (QALY) – but came to widely differing final estimates. These ranged from about £10,000 per QALY (an estimate derived from commercial-inconfidence data supplied by one of the manufacturers) to over $3 million per QALY (an American research group's findings). These estimates were very sensitive to assumptions made in the modelling process including, in particular, the impact of a relapse on quality of life and the time horizon over which benefits from therapy may be accrued. In addition the Committee recognised that uncertainties in the data or methods used were liable to magnification in

the extrapolation of the benefit beyond the duration of clinical trial-based treatment data.

4.10 The Committee therefore resolved that in the absence of further economic modelling it would be very difficult to make a recommendation on the cost effectiveness of these medicines with any confidence. The Institute commissioned a new cost-effectiveness analysis that was designed to address the problems associated with existing models. In doing so the Institute sought a maximum of cooperation between the group undertaking the new modelling ('the Consortium') and the consultees. This was designed both to help reconcile views on the model design and to ensure that the consultees were able to supply appropriate data to the Consortium. In the event, additional data for the new analysis were provided by Schering and Biogen. Data were provided but subsequently withdrawn by TEVA. No data were provided by Serono.

4.11 The new analysis compared treated patients' experience of both relapse and progression with the natural history of the disease. It examined the effects of using different time horizons and showed that the estimated mean cost per QALY gained (CQG) from treatment fell as the time horizon was lengthened. Shorter time horizons such as 5 years require less extrapolation from trial data but ignore possible gains resulting from the postponement of later, more debilitating, stages of the disease. On the other hand, lengthening the time horizon successively to 10 and 20 years increases the extrapolation error but includes more of the possible gains from postponement of later more debilitating stages of the disease. The Committee took the view that extrapolation errors for time periods over 20 years, more than double the period for which clinical data for patients on therapy are available, were so great that it could not consider estimates of cost effectiveness beyond 20 years. The Committee therefore considered only the three time horizons of 5,10 and 20 years.

4.12 While the Committee recognised that the extrapolation problem grows significantly as the time horizon increases, it nevertheless considered carefully estimates for each time frame. Estimated mean CQGs for 5- and 10-year time frames where higher (ranging from £380,000 to £780,000 for the 5-year model, and from £190,000 to £425,000 for the 10-year model) than for the 20-year time frame. At 20 years, using the results of the additional modelling, the

estimated mean CQG ranged from £40,000 to £90,000 for the four products considered.

4.13 In response to both manufacturers' and patient/carer organisations' comments, further analysis of the Consortium model was undertaken. An important component of this further review was the consideration of new observational data from a large survey conducted by the MS Research Trust (MSRT) of people with MS and their carers. This large survey used a questionnaire sent to a group of their members, who volunteered to provide personal details, characteristics of the form of MS (type of disease, number and frequency of relapses, EDSS score, presence of difficulties of cognition), and whether they were taking a beta interferon or glatiramer). The survey elicited quality-of-life information using the EQ-5D instrument (from which utility estimates may be derived). The survey which had been directed at people with whom the Trust had had some contact since its inception in 1993, and to which there were 1555 respondents, covered all MS types, including benign and primary progressive. In a number of responses the type of MS was not stated. Of the respondents, 152 were receiving treatment with one of the products considered in this appraisal at the time of the questionnaire.

4.14 The Consortium was asked to advise the Committee on whether the MSRT dataset was suitable for use within the model and if so, to advise on its effects on the model's estimates of CQG. The Consortium confirmed that the MSRT questionnaire results improve the database on utilities for EDSS states. However, further analysis of these data by the Consortium did not provide conclusive evidence of an effect of treatment on utility that was not already encapsulated in EDSS scores and relapse. The Consortium advised the Committee that they considered that the application of the appropriate population from the MSRT utilities dataset to their original model was valid and that they had now done this.

4.15 Benefit, measured in terms of disease progression, accrues whilst a patient is on treatment. When treatment stops (by 10 years for most patients), the model assumes that disease progression continues at a rate consistent with the natural history of the condition. Additionally, the model assumes that the treated group maintain benefit after cessation of treatment whilst incurring no additional treatment costs. Therefore, incorporating in the model the MSRT utilities data-set, the estimated CQG at 20 years (the time frame of the model) is between

£35,000 and £104,000. However, as there is no evidence on the long-term progression of patients after cessation of therapy, it remains possible that the additional benefit on therapy is not maintained when treatment stops. In this case, the CQG will increase. For example, if all benefit ceases after treatment stops at 10 years, the estimated CQG after 20 years would be between £120,000 and £339,000.

4.16 In response to requests from some consultees, the Committee also examined the modelling of approaches in which therapy would begin at progressively higher levels of EDSS. While these approaches lowered the estimated mean CQG substantially, the Committee concluded that this result was a product of the assumption in the model relating to disease progression off treatment at later time periods.

Consideration

4.17 Given the nature of the disease, considering the effects of treatment beyond the end of therapy is appropriate. Without data that measure such effects modelling is required. The results will reflect the underlying uncertainty of the assumptions that underpin the model. The Committee was encouraged, by consultees, to consider time horizons of 20 years and beyond in this condition although the maximum extent of published observations of disease progression in treated patients in MS is 8 years.

4.18 The new economic modelling incorporated two key assumptions: (a) continuing benefit on treatment and (b) on discontinuation of treatment, a return to a rate of progression equivalent to the natural history of the disease. Both of these assumptions become increasingly unreliable as the time horizon is increased.

4.19 The results of modelling approaches in which therapy would begin at progressively higher levels of EDSS are products of the assumption in the model relating to disease progression off treatment at later time periods and therefore do not constitute a suitable basis for formulating guidance.

4.20 The CQG estimates in paragraph 4.15 will be reduced by the inclusion of the effects on personal social service costs. In considering comments from consultees, the Committee took the view that the improvement in the estimates

of CQG, even if such effects were assumed to be as much as 15%, would not materially affect their conclusion.

4.21 In its deliberations on cost effectiveness the Committee was mindful of the various criticisms of QALYs in general and their use in this specific context. Some of these issues are addressed in Appendix E.

4.22 The Committee, in its appraisals of health technologies, is required to consider the broad balance between benefits and costs. In doing so, it must consider not only the cost effectiveness of the particular technology under consideration, but where that cost effectiveness stands relative to treatments for other conditions. The Committee found no measures other than QALYs that could better assist in its responsibility to make a judgement about the 'balance of costs and benefits'. The estimates in paragraph 4.15 constitute the best available evidence.

4.23 Long-term extrapolation of treatment benefit after cessation of therapy is not supported by evidence. The Committee therefore decided that its conclusion on the cost effectiveness of these products must take account of the uncertainty associated with an assumption that treatment benefit is maintained for 10 years or more after cessation of therapy. On the balance of costs and benefits, the beta interferons and glatiramer acetate are not cost effective. In reaching this conclusion, the Committee had in mind the cost-effectiveness ratios of the technologies which the Institute has previously recommended for use in the NHS in England and Wales.

4.24 In arriving at this conclusion, the Appraisal Committee took account of the Directions to the Institute laid out by the Secretary of State for Health. Those Directions require the Institute to take into account inter alia the degree of clinical need of people with the condition, the broad balance of benefits and costs and the efficient use of NHS resources. The Institute did not receive guidance from the Secretary of State or the National Assembly for Wales on the resources that may be available for these medicines.

4.25 The Committee considered the view that there was no valid basis for distinguishing guidance between patients currently receiving treatment with one of these medicines and other patients. This would have the implication that patients currently being prescribed a beta interferon or glatiramer should have no greater access to therapy than others. The Committee felt that this view

must be balanced against other considerations such as the existing, at least implicit, patient-doctor agreement to continue therapy once started and the potential loss of well being that might follow from unanticipated treatment changes. The Committee concluded that these were relevant factors, which patients currently receiving beta interferon or glatiramer acetate for MS and their consultants might bear in mind when considering this guidance. Consultants and their patients might reasonably conclude that therapy should not be withdrawn as a result of this guidance but that they should continue treatment until individual patients and their consultants consider it is appropriate to stop, having regard to the criteria established for withdrawal from treatment in the Guidelines of the Association of British Neurologists published in January 2001.

4.26 Other than disease-modifying treatments, management strategies for MS are aimed at ameliorating symptoms, in order to allow the patient to maintain an optimal quality of life, as presently there is no cure for the disease. The Committee is aware that the Institute has commissioned a clinical guideline on the management of MS. It is also aware that this guideline will examine and make recommendations on the range of interventions available for people with this disease.

5 Further research

5.1 Trusts and health authorities are encouraged to collect data on all people with MS who continue on beta interferon or glatiramer as indicated in paragraph 1.2. The data collected could usefully include details of the patient and the reason they are receiving treatment. It would be helpful also to record the preparation used, the patient's relapse frequency and disease progression while on treatment, the development of adverse effects and neutralising antibodies, compliance with the therapy, the reasons for discontinuing therapy and the subsequent rate of progression of the disease.

6 Implications for the NHS

6.1 On the basis of the recommendations in Section 1, but subject to any developments resulting from the implementation advice in Section 7.1 below, it is not expected that this guidance will result in a material change in current expenditure on these medicines.

7 Implementation

7.1 The Committee considered that the Department of Health, the National Assembly for Wales and manufacturers, might usefully consider what actions could be taken, jointly, to enable any of the four medicines appraised for this guidance to be secured for patients in the NHS in England and Wales, in a manner which could be considered to be cost effective. Unless further evidence emerges which reveals a significant improvement in their clinical effectiveness, the cost-effectiveness of these medicines can only be improved if there is a significant reduction in the total cost of their acquisition by the NHS in England and Wales. The uncertainty surrounding the definition of which patients benefit and to what extent, together with the ability of the NHS to identify a total potential patient population for which these medicines might most beneficially be purchased, are factors which could be considered relevant in any discussions between the Department of Health and the National Assembly for Wales and manufacturers on ways in which these medicines could be acquired cost effectively. The Committee noted that the results of the additional economic modelling commissioned by the Institute revealed that interferon beta-1b (Betaferon, Schering) is, currently, the most cost effective of the four products appraised for this guidance.

7.2 Further guidance on audit of the care provided to people with MS is forthcoming with the publication by the Institute of a clinical guideline on the management of MS.

8 Related guidance

8.1 The Institute produced a full clinical guideline on the management of Multiple sclerosis (NICE clinical guideline 8) (2003).

9 Review of guidance

9.1 Information on the review of the guidance on this technology is available on the NICE website

9.2 Should any significant new evidence of clinical effectiveness or a re-evaluation of published or unpublished clinical data become available, or if there were to be a substantial change in unit costs or other actions, which led to a significant change in the cost effectiveness of the beta interferons or glatiramer, this new information will be considered by the Institute. A judgement will be made at that time as to whether such evidence should result in an earlier review of this guidance.

Andrew Dillon
Chief Executive
January 2002

Appendix A. Appraisal committee members

The Appraisal Committee is a statutory committee whose members sit for 3 years. Two meetings are held per month and the majority of members attend one or the other. Declared interests may also exclude a member from individual technology appraisals. The committee are supplemented by technology specific experts as indicated in Appendix B.

Professor R. L. Akehurst
Dean, School of Health Related Research Sheffield University

Professor David Barnett (Chairman)
Professor of Clinical Pharmacology University of Leicester

Professor Sir Colin Berry
Professor of Morbid Anatomy St Bartholomew's and Royal London School of Medicine

Dr Sheila Bird
MRC Biostatistics Unit, Cambridge

Dr Karl Claxton
Lecturer in Economics University of York

Professor Duncan Colin-Jones
Professor of Gastroenterology University of Southampton

Professor Sarah Cowley
Professor of Community Practice Development Kings College, London

Dr Nicky Cullum
Reader in Health Studies University of York

Mr Chris Evennett
Chief Executive Mid-Hampshire Primary Care Group

Professor Terry Feest
Clinical Director and Consultant Nephrologist Richard Bright Renal Unit and Chairman of the UK Renal Registry

Ms Jean Gaffin
Formerly Executive Director National Council for Hospice and Specialist Palliative Care Service

Mrs Sue Gallagher
Chief Executive Merton, Sutton and Wandsworth Health Authority

Dr Trevor Gibbs
Head, Global Clinical Safety & Pharmacovigilance GlaxoSmithKline

Mr John Goulston
Director of Finance The Royal Free Hampstead NHS Trust

Professor Philip Home
Professor of Diabetes Medicine University of Newcastle

Dr Terry John
General Practitioner The Firs, London

Dr Diane Ketley
Research into Practice Programme Leader NHS Modernisation Agency

Dr Mayur Lakhani
General Practitioner, Highgate Surgery, Leicester and Lecturer, University of Leicester

Mr M Mughal
Consultant Surgeon Chorley and South Ribble NHS Trust

Mr James Partridge
Chief Executive Changing Faces

Professor Philip Routledge
Professor of Clinical Pharmacology University of Wales

Professor Andrew Stevens (Vice Chairman)
Professor of Public Health University of Birmingham

Dr Cathryn Thomas
General Practitioner Senior Lecturer Department of Primary Care and General Practice University of Birmingham

Appendix B. Sources of evidence

1. The following documentation and opinion were made available to the Committee

a. Assessment Report:

Prepared by the Northern and Yorkshire Regional Drug & Therapeutics Centre (*Assessment of Interferon-Beta and Glatiramer for the Treatment of Multiple Sclerosis*, April 2000).

b. Additional economic modelling:

ScHARR Consortium Final Report to the National Institute for Clinical Excellence (*Cost effectiveness of beta interferons and glatiramer acetate in the management of multiple sclerosis*), Centre for Bayesian Statistics in Health Economics, School of Health and Related Research (ScHARR), University of Sheffield.

c. Manufacturer/sponso submissions:

- Aventis Pharma Limited
- Biogen Limited
- Schering Health Care Limited
- Serono Pharmaceuticals Limited
- Teva Pharmaceuticals Limited

d. Professional/specialist group submissions:

- Association of British Neurologists
- Chartered Society of Physiotherapy
- Royal College of Nursing
- Royal College of Physicians
- Royal College of General Practitioners

e. Patient group submissions:

- Multiple Sclerosis Research Trust
- Multiple Sclerosis Society
- Neurological Alliance

f. External expert and patient advocate submissions:

- Mr Peter Cardy, Chief Executive and others representing the Multiple Sclerosis Society
- Professor Alastair Compston, University Department of Neurology, Addenbrooke's NHS Trust
- Ms Christine Jones and others representing the Multiple Sclerosis Research Trust
- Professor Alan Thompson, Garfield Weston Professor of Clinical Rehabilitation, The National Hospital for Neurology and Rehabilitation and Medical Advisor to the Multiple Sclerosis Society
- Dr John Zajicek, Consultant Neurologist and Honorary Senior Lecturer, Plymouth Postgraduate Medical School

Appendix C. Beta interferon and glatiramer acetate for the treatment of multiple sclerosis – information for patients

'Understanding NICE Guidance', a summary of this guidance for patients and carers can be found on our website.

Appendix D. Expanded Disability Status Scale

0.0	Normal neurological exam (all grade 0 in Functional Systems [FS]; Cerebral grade 1 acceptable.
1.0	No disability, minimal signs in one FS (i.e. grade 1 excluding Cerebral grade 1).
1.5	No disability minimal signs in more than one FS (more than one grade 1 excluding Cerebral grade 1).
2.0	Minimal disability in one FS (one FS grade 2, others 0 or 1).
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1).
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory.
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1).
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 500 metres.
4.5	Fully ambulatory without aid, up and about much of the day, able to work a fully day, may otherwise have some limitation of full activity or require minimal assistance; characterised by relatively severe disability, usually consisting of one FS grade 4 (others 0 to 1) or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 300 metres.
5.0	Ambulatory without aid or rest for about 200 metres; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 to 1; or combinations of lesser grades usually exceeding specifications for step 4.0).
5.5	Ambulatory without aid or rest for about 100 metres; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding those for steps 4.0).
6.0	Intermittent or unilateral constant assistance (cane, crutch or braces) required to walk about 100 metres with or without resting. (Usual FS equivalents are combinations with more than two FS grade 3+).

6.5	Constant bilateral assistance (canes, crutches or braces) required to walk about 20 metres without resting. (Usual FS equivalents are combinations with more than two FS grade 3+).
7.0	Unable to walk beyond about 5 metres even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day. (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely, pyramidal grade 5 alone).
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; maintains many self-care functions; generally has effective use of arms. (Usual FS equivalents are combinations, generally grade 4+ in several systems).
8.5	Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self care functions. (Usual FS equivalents are combinations, generally 4+ in several systems).
9.0	Helpless bed patient; can communicate and eat. (Usual FS equivalents are combinations, mostly grade 4+).
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow. (Usual FS equivalents are combinations, almost all grade 4+).
10.0	Death due to MS.

Appendix E. Measurement of health benefits

This Appendix, taken with modifications from the Evaluation Report to the Appraisals Committee, provides some background information on the way in which health benefits are calculated. It does not form part of the guidance proper.

A1 Measuring benefits

A1.1 Measures of the benefit of treatment used in cost-effectiveness analyses can be based on 'natural' units, for example years of life gained, or on value-based measures, for example Quality Adjusted Life Years (QALYs). The number of QALYs gained by using a particular treatment is a measure of its benefit in terms of improvements in the quality of life of patients (including physical performance, pain, distress and psychological improvements as well as changes in survival) summed over a period of time. It therefore incorporates the value of changes in both morbidity and mortality, where these exist.

A1.2 In the particular case of MS, although there are natural units which capture specific aspects of the impact of MS, such as relapses avoided and delaying progression to wheelchair dependency, there is none which captures both the impact on relapses and the full impact of progression. These measures therefore ignore some of the established benefits of the beta interferons.

A1.3 Although imperfect as 'natural' units to capture gains from delayed progression, the EDSS does provide a means to create a value-based measure of benefit. All of the studies that attempt to encompass the full effect of delayed progression have used changes in EDSS converted to changes in QALYs. This requires an estimate of utilities (adjustments for level of quality of life) applied to each of the EDSS levels, and based not on the disability itself but to include all the associated morbidity.

A1.4 An alternative measure is provided in the literature and in the submissions in the form of a measure based on the EDSS called variously Area Under the Curve, integrated area under the EDSS time curve or disability burden unit. This is calculated by multiplying the EDSS score by the time during which that score is observed, and summing over time. This measure is therefore very similar to the QALY, the difference being that EDSS scores are given an equal weight rather than a weight based on the relative utility of different health states.

A1.5 This summed EDSS measure has a number of disadvantages. The numbers used in the EDSS itself are not cardinal numbers either by construction or by behaviour. (A "cardinal" number can be added, subtracted, multiplied or divided, and the result has ready meaning.) The EDSS score is, by

contrast, "ordinal", which means that a higher score represents greater disability. But it does not imply, for example, that an EDSS score of 8 (restricted to bed or chair or perambulated in a wheelchair) is twice as disabled a state as an EDSS score of 4 (fully ambulatory and able to walk up to 500 metres without aid or rest). This means that the summed EDSS measure is also not cardinal. Its units are arbitrary, meaning that a cost per summed EDSS score avoided is equally arbitrary. The utility scores used in calculating QALYs weight the underlying EDSS scores in ways designed to produce cardinal numbers having identifiable units. The summed EDSS score therefore shares any problems that the QALY has and has a number of others besides.

A2 The use of QALYs in MS

A.2.1 Although all of the submissions to the Committee from the manufacturers report QALYs and cost-effectiveness ratios derived from them, some also make a number of criticisms of the approach. These include some unexplained "assertions", but the following statements warrant further comment:

A.2.2 QALYS discriminate against people with MS.

This appears to be based on two premises. The first is a mistaken belief that QALY measurement does not count transient improvements in quality of life; that is emphatically not the case. The second is a related argument that people with disabilities do not have the same potential to gain QALYs because of their lower underlying quality of life. However, this argument only applies, and then in theory only, to therapies that are lifesaving. It does not apply to interventions that improve quality of life – on the contrary, lower quality of life suggests a greater capacity to gain QALYs. Since the impact of therapies for MS is dominated by improvements in quality of life, this criticism does not apply.

A.2.3 QALYs do not discriminate in favour of people with MS.

The QALY approach is egalitarian in considering any particular gain in quantity or quality of life as being of equal value regardless of the age, sex or other characteristics of the recipients The suggestion is that QALYs should be adjusted so that they are greater for those of working age. In other words, it proposes that one should discriminate against young and old people, because they do not work or have dependants. Whilst there is some evidence that there are those who would support such discrimination, it is unclear how far it should be taken. A logical implication of the argument in favour of such discrimination is that QALYs should be weighted against individuals of working age who do not have dependants or who are unable to work. It might even imply

employment of an individual weight based on the number of dependants and the size of income from employment.

A.2.4 QALY gains are estimated using a population based estimate of utility values, which are inferior to those based on patient preferences.

The evidence provided by Parkin *et al (J of Neurology,Neurosurgery and Psychiatry*, 2000; 68: 144-49) suggested that despite differences in utility values for health states, estimates of QALY gains were not affected by the use of patient rather than population utilities. Moreover, there is an argument that societal-based estimates used consistently for all evaluations are more appropriate because they reflect wider values that are comparable over different therapies.

A.2.5 QALY gains include average relapses and therefore do not take account of severe relapses.

This is not correct, since the calculation of an average includes both more severe and milder relapses as well as those of average severity. A larger sample of people with MS, thus containing more relapses than that which has been studied to date, might include a greater number of severe relapses and might plausibly raise the average severity. However, it may also include a smaller proportion of severe relapses and so lower average severity. There is no evidence either way.

A.2.6 The loss of utility due to relapses may be an underestimate because it is assessed after the event.

This may be true; there are methodological difficulties with obtaining quality of life data during relapses that are serious enough to require hospitalisation, which mean that it is difficult to test. However, there is no evidence that the values are too high, or too low.

Changes after publication

March 2014: minor maintenance

March 2012: minor maintenance

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

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The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

GJMT coordinated the project, led the review of clinical effectiveness and led the drafting of the report. PA led the review of cost effectiveness, the critique of the RSS submission and the economic modelling and contributed to drafting the report. XA co-led the review of clinical effectiveness and contributed to the drafting of the report. HM and JM contributed to the economic evaluation work and contributed to drafting the report. RC contributed to the reviews of clinical and cost effectiveness through search and information specialist support and to the drafting of the report. AK and SL contributed to the review of clinical effectiveness and to the drafting of the report. CC and OC contributed as clinical experts and to the drafting of the report. JP and JR contributed to the review of clinical effectiveness and to the drafting of the report. HF contributed to drafting the report. AC supervised the project and contributed to the drafting of the report.

Please refer to the International Committee of Medical Journal Editors (ICMJE) ***Uniform Requirements for Manuscripts Submitted to Biomedical Journals see*** *http://www.icmje.org/*

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1 ABSTRACT

Aims and objectives

To undertake:

a) systematic reviews of clinical and cost effectiveness of disease modifying therapies (DMTs) (Interferon β-1a, Pegylated interferon β-1a, Interferon β-1b and Glatiramer acetate) in relapsing remitting multiple sclerosis, secondary progressive multiple sclerosis and clinically isolated syndrome, against best supportive care (BSC) and each other investigating annualised relapse rate (ARR), and time to progression at 3 months (TTP3) and 6 months (TTP6);

b) cost effectiveness assessments of DMTs for CIS and RRMS against BSC and each other; to update NICE Technology Appraisal (TA) 32.

Methods

Searches were undertaken in January and February 2016. Databases included the Cochrane Library, MEDLINE, and the Science Citation Index. Two reviewers screened and assessed titles and abstracts with recourse to a third when needed. The Cochrane risk of bias tool and CHEERS and Phillips checklists were used for appraisal. Narrative synthesis and, where possible, random effects meta-analysis and network meta-analysis (NMA) were performed.

Cost effectiveness analysis used published literature, an updated RSS model (based on the UK Department of Health Risk Sharing Scheme observational study with historical comparator) and expert opinion. A de novo economic model was built for CIS. The base case used updated RSS data, an NHS and PSS perspective, 50-year time horizon, 2014/2015 prices and a discount rate of 3.5%. Outcomes are reported as incremental cost-effectiveness ratios (ICERs) as cost per quality-adjusted life year gained. Models were run deterministically with sensitivity analyses and probabilistically with 1,000 bootstrapped iterations.

Results

We included 63 publications relating to 35 RCTs. 83% had high risk of bias. There was very little difference between the different drugs in reducing moderate or severe relapse rates in RRMS. All were beneficial against BSC giving a pooled rate ratio of 0.65 (95% CI [0.56, 0.76]) for annualised relapse rate (ARR) and an HR of 0.70 (95% CI [0.55, 0.87]) for TTP3. NMA suggested Glatiramer acetate 20 mg SC had the highest probability of being the best in reducing ARR.

Three separate cost effectiveness searches resulted in > 2,500 publications with 26 included studies informing narrative synthesis and model inputs. The base case using a modified RSS gave mean incremental costs of £25,600 for pooled DMTs compared to BSC and 0.943 more QALYs to give an ICER of £27,200 per QALY. Probabilistic sensitivity analysis gave an ICER of £32,000 per QALY. AG inputs gave an ICER of £8,100 per QALY for pooled DMTs versus BSC. Pegylated IFN β-1a 125µg (Plegridy) was the most cost effective option of the individual DMTs with an ICER of £7000 compared to BSC. Glatiramer acetate 20 mg (Copaxone) was most cost effective treatment for CIS with an ICER of £12,900 per QALY gained.

Discussion and conclusions

DMTs both separately and together are clinically and cost effective for treatment of both RRMS and CIS. Both RCT evidence and the DH RSS data are at high risk of bias. Research priorities include comparative studies with longer follow up and systematic review and meta-synthesis of qualitative studies.

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2 LIST OF ABBREVIATIONSAND STATISTICAL GLOSSARY

Technical terms and abbreviations are used throughout this report.

ABN	Association of British Neurologists
AIC	Akaike information criterion
AMSTAR	Assessing the methodological qualities of systematic reviews
ANOVA	Analysis of variance
ARR	Annualised relapse rate
AUD	Austrailian dollars
BCMS	British Columbia Multiple Sclerosis Database
BIC	Bayesian information criterion
BNF	British National Formulary
BOI	Burden of illness
BSC	Best standard care
CDMS	Clinically definite multiple sclerosis
CEA	Cost-effectiveness analysis
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence interval
CIS	Clinically isolated syndrome
CSF	Cerebrospinal fluid
CNS	Central Nervous System
DH	UK Department of Health
DIS	Disseminated in space
DIT	Disseminated in time
DMF	Delayed-release dimethyl fumarate
DMTs	Disease modifying therapies
DSS	Disability Status Score
EBV	Epstein-Barr Virus
EDSS	Expanded disability status scale
ESG	European Study Group
EQ-5D	Euro Quality of Life 5 dimensions questionnaire
GA	Glatiramer Acetate
GPRD	General Practice Research Database
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GWAS	Genome-wide association studies
HCHS	Hospital and Community Health Services
HLA	Human leucocyte
HR	Hazard ratio
HRQoL	Health related quality of life

HUI	Health Utility Index
ICER	Incremental cost-effectiveness ratio
IFN	Interferons
IM	Intramuscular
INHS	Italian National Health Service
LYG	Life-years gained
MBP	Myelin basic protein
MLY	Mono-symptomatic life years
MRI	Magnetic resonance imaging
MS	Multiple Sclerosis
MSCRG	Multiple Sclerosis Collaborative Research Group
MTA	Multiple Technology Appraisal
NABs	Neutralising antibodies
NASG	North American Study Group
NAWM	Normal-appearing white matter
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
ONS	Office of National Statistics
PASAT	Paced Auditory Serial Addition Test
PEG	Polyethylene glycol
pegIFN-β-1a	Pegylated IFN-β-1a
PPMS	Primary Progressive multiple sclerosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRMS	Progressive relapsing multiple sclerosis
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALYs	Quality Adjusted Life Years
QoL	Quality of life
RR	Rate ratio
RCT	Randomised controlled trial
RePEC	Research Papers in Economics
RRMS	Relapsing remitting multiple sclerosis
RSS	Risk sharing scheme
SC	Subcutaneous
ScHARR	School of Health and Related Research
SEKs	Swedish Kroners
SMR	Standardized mortality rates

SNPs	Single-nucleotide polymorphisms
SPMS	Secondary progressive multiple sclerosis
S(t)	Survival at time t
SUCRA	Surface Under the Cumulative Ranking Curve
SWIMS	South West Impact of Multiple Sclerosis
TA32	Technology appraisal guidance 32
TTP	Time to progression
UK	United Kingdom
WTP	Willingness-to-pay

Statistical glossary

Annualised relapse rate (ARR). This indicates the number of relapses a patient would expect to have on average every year. Differences in the annualised relapse rate are measured as a rate ratio, which suggests the percentage difference in rate between two groups. That is, a rate ratio of 0.75 in group 1 as compared to group 2 means that group 1 has 25% fewer relapses than group 2. In contrast, a rate ratio of 1.25 suggests than group 1 has 25% more relapses than group 2. In MS, an improvement of one drug over another would be represented by a rate ratio of less than 1.

Time to disability progression (TTP). This indicates how quickly a patient would expect to have disability progression compared to another patient. This is measured as a hazard ratio. A hazard ratio less than 1 in group 1 as compared to group 2 means that group 1 will take longer to have disability progression. Conversely, a hazard ratio greater than 1 in group 1 as compared to group 2 means that group 1 will have disability progression faster on average. For example, a hazard ratio of 0.75 in group 1 as compared to group 2 means that at a point in the future, people without progression group 1 will have a 25% less chance of having disability progression as compared to people without progression in group 2. In MS, an improvement of one drug over another would be represented by a hazard ratio of less than 1.

Time to disability progression confirmed at 3 (or 6) months (TTP3 or TTP6). To reduce the effect of 'blips' in disability progression on estimates of effectiveness, many trials require than an initial sign of disability progression be confirmed at a repeat visit 3 (or 6) months later. Thus, time to disability progression confirmed at 3 months is simply the time to disability progression, when that disability progression has been subsequently confirmed 3 months after the visit where progression was first detected. Similarly, time to disability progression confirmed at 6 months is the time to progression when that progression has been subsequently confirmed 6 months after the visit where it was first detected.

Surface under the cumulative ranking curve (SUCRA). In network meta-analysis, it is possible to rank interventions on the size of their effect. This is done using the surface under the cumulative ranking curve, or the SUCRA. A higher SUCRA means a larger magnitude of effect. For clinical effectiveness outcomes, such as relapse rate and time to disability progression, interventions are ranked based on how much the intervention reduces relapse or slows down disability progression. For discontinuation due to adverse events, interventions are ranked on how much they increase the risk of discontinuation.

3 PLAIN ENGLISH SUMMARY

Multiple sclerosis (MS) causes inflammation of the nerves. It is a leading cause of disability in the UK. This study is about two types of MS. In relapsing remitting MS (RRMS) people have relapses, or attacks of more severe illness and recovery. In clinically isolated syndrome (CIS) people have just one episode but are thought to be at high risk of developing MS.

Various treatments are available for RRMS and CIS, including different types of beta interferons and glatiramer. These are known as disease-modifying therapies. In this study we looked at the clinical effectiveness and cost effectiveness of these drugs for RRMS and CIS.

We carried out systematic reviews of randomised controlled trials. We pooled the results on relapse rates and time to worsening of the disease. We drew on a Risk Sharing Scheme set up by the Department of Health to collect long-term information on the disease modifying therapies. We developed our own model for CIS.

We found that all the disease-modifying therapies were clinically and cost effective in both RRMS and CIS. The studies were at high risk of bias and had short follow up. A longer-acting interferon (Plegridy) was the most cost effective option for RRMS and glatiramer was the most cost effective for CIS.

We think that longer-term research is needed comparing these drugs with each other. A review of qualitative studies is also needed so we can understand more about the preferences and experiences of people living with MS.

4 SCIENTIFIC SUMMARY

4.1 *Background*

Multiple sclerosis (MS) is a neurodegenerative disorder characterized by inflammation and demyelination of neurons in the brain and spinal cord. It is a leading cause of disability in working-age adults, and affects over 100,000 people in the UK. The commonest form of MS is relapsing remitting MS or RRMS. A single demyelinating event thought to precede MS is known as clinically isolated syndrome (CIS) and RRMS can progress to secondary progressive MS (SPMS). Although there is currently no cure for MS, there are a number of disease-modifying therapies (DMTs) available to help reduce the frequency of relapses and the rate of disease progression. Beta interferons (IFN-β) and glatiramer acetate (GA) are two such drugs. At the time of the most recent NICE Technology Appraisal guidance on these drugs (TA32) in 2002, there was insufficient evidence of their clinical and cost-effectiveness. A risk-sharing scheme was put in place, allowing patients to access the drugs and the NHS to adjust prices based on cost-effectiveness data, as well as to monitor long-term outcomes. This current study aims to appraise the clinical and cost-effectiveness of IFN-β and glatiramer acetate, for MS integrating published evidence with data from the risk-sharing scheme and also to assess their role in CIS.

4.2 *Decision problem*

Our objectives were: a) to systematically review the evidence for the clinical effectiveness of

- IFN β-1a;
- Pegylated IFN β-1a;
- IFN β-1b; and
- GA

in people with

- relapsing multiple sclerosis (including people with relapsing remitting multiple sclerosis and people with secondary progressive multiple sclerosis with active disease, evidenced by relapses), and
- clinically isolated syndrome, that is, a single demyelinating event, who are considered at high risk of developing subsequent multiple sclerosis;

against the following comparators:

- best supportive care without disease modifying treatment, and
- beta interferons and glatiramer acetate compared with each other;

and investigating the following outcomes:

- relapse rate;
- transition to clinically definite MS, in the case of CIS;

- severity of relapse;
- disability (for example, expanded disability status scale [EDSS]);
- symptoms of multiple sclerosis such as fatigue, cognition and visual disturbance;
- freedom from disease activity;
- discontinuation due to neutralising antibodies;
- mortality;
- adverse effects of treatment; and
- health-related quality of life;

and b) to systematically review existing economic evaluations, including use of the existing RSS model; to develop a *de novo* economic model for CIS; to assess the cost effectiveness of the treatments (IFN β-1a, pegylated IFN β-1a, IFN β-1b, and GA) in treatment of CIS and RRMS against the stated comparators, expressed in incremental costs per quality-adjusted life year, with a time horizon sufficiently long to reflect any differences in costs or outcomes between the technologies being compared and from an NHS and Personal Social Services perspective; and to update model parameters and inputs to reflect available evidence from the literature, current costs, the NICE reference case, current practice, and new data from the risk sharing scheme.

4.3 *Methods*

4.3.1 Clinical and cost-effectiveness reviews

Searches were undertaken in January and February 2016. Several relevant systematic reviews were identified for some populations and study types, allowing some searches to be limited by publication date to 2012 onwards. For those populations and study types where no suitable systematic reviews were identified, database searches were undertaken from inception. Databases included were the Cochrane Library, the Cochrane MS specialized register; MEDLINE; Embase and the Science Citation Index. For the cost effectiveness reviews the NHS EED, Research Papers in Economics (RePEC) and the Cost-effectiveness Analysis (CEA) Registry were included. Online trials registers were searched as well as websites for Companies, Patient and carer, Professional and Research groups. Included designs were RCTs, systematic reviews, meta-analyses and cost-effectiveness studies. The population was people diagnosed with RRMS, SPMS, or CIS and the intervention was one of the designated drugs used within its marketing authorisation (and including the recommended dose regimen). Searches of reference lists and information provided by the manufacturers for the interventions were checked for additional eligible studies. Two reviewers screened and assessed titles and abstracts of all records for inclusion independently with recourse to a third reviewer in cases of disagreement. Systematic reviews used to locate primary studies were appraised using the AMSTAR checklist, primary clinical effectiveness studies were appraised using the Cochrane risk of bias assessment tool and health economic studies with the CHEERS and Phillips checklists. Narrative synthesis was undertaken. Where possible random effects meta-analyses and network meta-analyses were performed using Stata v14 for each outcome.

4.3.2 Cost-effectiveness methods

The RSS model is an economic analysis conducted to assess the cost-effectiveness of the combined treatment effect of disease modifying treatments included in the Risk Sharing Scheme (RSS) compared with best supportive care for people with relapsing-remitting multiple sclerosis. It is a Markov model based on the British Columbia multiple sclerosis (BCMS) cohort for natural history compared with cohorts of patients taking the intervention drugs. Drug prices were agreed with the Department of Health (DH) as part of the Risk Sharing Scheme. We based our cost effectiveness analysis on the RSS model, including data from the ten year follow up where available. For CIS we built a *de novo* economic model to assess the cost-effectiveness of the identified drugs. We used outcome values derived from our systematic reviews of the published literature, RSS pooled cost-effectiveness data, data submitted by the companies, expert opinion and NHS reference costs to input into the models in order to understand the relative costs and effectiveness of the different interventions and to explore the different assumptions made.

We used our modified RSS model with clinical effectiveness inputs derived from the Year 10 RSS analyses as the base case for RRMS with additional evidence on time to progression for the CIS base case. We estimated mean total costs and mean total QALYs for each intervention compared with best supportive care (BSC) and with each other and adopted an NHS and PSS perspective with a 50-year time horizon. Costs were in 2014/5 prices and a discount rate of 3.5% was used. Outcomes are reported as incremental cost-effectiveness ratios expressed in terms of cost per quality-adjusted life year gained. The models were run deterministically. We undertook sensitivity analyses and explored uncertainty to investigate key drivers. For RRMS we undertook probabilistic analyses with 1,000 bootstrapped iterations.

4.4 *Results*

4.4.1 Clinical effectiveness results

We identified 6,419 publications of which we included 63 relating to 35 primary studies. 83% (30/35) were at high risk of bias from either complete or partial participant unblinding and studies also suffered from relatively short follow-up times. Five studies investigated DMTs for CIS all demonstrating a benefit in time to progression to MS when compared against placebo or BSC. Three trials investigated SPMS indicating benefit from the interventions against placebo and 27 compared different DMTs with each other or placebo for RRMS using a variety of outcomes. In RRMS there was very little difference between the different drugs in reducing moderate or severe relapse rates. Random effects network meta-analysis gave a pooled rate ratio of 0.65 (95% CI 0.56, 0.76) for annualised relapse rate (ARR) for all intervention drugs compared to placebo and an HR of 0.70 (95% CI 0.55, 0.87) for disability progression confirmed at three months (TTP3). Rankings suggested that the drug which had the highest probability of being the best in reducing ARR was glatiramer acetate 20 mg SC once daily, followed by pegylated IFN β-1a 125 µg SC every two weeks. For TTP3 IFN β-1a 44 µg SC thrice weekly had the highest probability of being the most effective.

4.4.2 Cost effectiveness results

Our searches for systematic reviews identified 1566 records of which nine were economic evaluation studies. Searches for economic evaluations in CIS revealed 614 records of which 9 were selected. Searches for primary cost-effectiveness, HRQoL, costs and resource use studies for DMTs in RRMS yielded 2451 studies of which 8 matched inclusion criteria. The cost-effectiveness systematic review findings suggested that models were sensitive to time horizons. Most demonstrated an acceptable ICER for different formulations of IFN β-1b in relation BSC at standard levels of willingness to pay in a number of different countries. For RRMS however findings were often not generalizable and, studies were sensitive to time horizons used and starting distributions of disability.

In the RSS model submission, a mean RR of 0.72 (95%CI Not reported) for ARR and a hazard ratio of 0.7913 (95%CI [0.7705, 0.8122]) for disability progression (equivalent to our TTP3 value) were given for patients taking DMTs compared to placebo based on year 10 analyses. Our base case using a modified RSS gave mean incremental costs of DMTs compared to BSC of approximately £25,600 more than BSC and produced 0.943 more QALYs to give an ICER of approximately £27,200 per QALY. Probabilistic sensitivity analysis gave similar values with an ICER of approximately £32,000 per QALY gained. DMTs were approximately £14,800 more costly than BSC using our clinical effectiveness results whilst conferring 1.822 more QALYs, equating to an ICER of approximately £8100 per QALY. Using the RSS base case model and with individual hazard ratios, we found that pegylated IFN β-1a 125 µg (Plegridy) was the most cost effective option with incremental costs of £17,800 and QALYs of 2.559 giving an ICER of £7000 compared to BSC. We explored varying key model input parameters, finding that changes to the hazard ratio for disability progression had the greatest impact on the cost-effectiveness results. A decrease in treatment effect (increase in hazard ratio by 10%) resulted in an ICER of approximately £64,000 per QALY gained.

For CIS we found that compared to BSC the optimal strategy was treatment with glatiramer acetate 20 mg (Copaxone) followed by DMTs for progression to RRMS. This was associated with incremental costs of £76,600 and incremental QALYs of 5.95 giving an ICER of £12,900 per QALY gained. Sensitivity analyses show that the model was most sensitive to change in the utility of the CIS health state. A 10% increase would however still give an ICER for glatiramer acetate 20 mg (Copaxone) of £14,500 versus best supportive care, well within the normal expected levels of willingness to pay.

4.5 Discussion and conclusion

We undertook systematic reviews, appraised the RSS model and designed a de novo model for CIS, to assess the clinical and cost effectiveness of DMTs in MS. From our systematic reviews we found that DMTs are effective when used for both RRMS and CIS. From our network meta-analysis glatiramer acetate is the most effective in reducing annualised relapse rate. For RRMS we found that overall DMTs are cost effective at current levels of willingness to pay at £27,200 per QALY. The individual drug with the lowest ICER against BSC at £7,000 was IFN β-1a 125 µg (Plegridy). We found that for CIS if DMTs are subsequently used for RRMS, the most cost effective option for CIS is glatiramer acetate.

4.5.1 Strengths and limitations

Strengths of the work include rigorous and comprehensive systematic reviews and a large number of network meta-analyses alongside careful assessment of company submissions and the RSS model. We built a de novo decision tree model to assess cost-effectiveness in CIS and for each investigation undertook a number of sensitivity analyses. Limitations include the limitations of the underlying studies, in that heterogeneity of definitions e.g. of progression, or of subgroups and of sparse networks limit our ability to synthesise our findings fully. More importantly we consider that the RCT evidence is problematic in that 30/35 studies were at high risk of bias and this along with short follow up times may not allow for adequate assessment of DMT effects. It is for these reasons that we elected to use a modified RSS model with appropriate adjustments, even though it is based on an observational design with a non-contemporaneous control cohort, as our base case for asssessment of cost effectiveness of the DMTs. In addition, in the cost effectiveness review we were unable to identify reliable estimates of utilities for CIS although we were able to take account of this in sensitivity analyses. The economic model represents the care pathway to the best of our knowledge, but practice and management may vary.

4.5.2 Implications for healthcare

We did not include formulations outside the recommended usage in the UK. Also we should recognise here that our study was specifically designed to exclude the clinical and cost-effectiveness of newer MS treatments such as newer monoclonal antibodies (alemtuzumab, daclizumab). This review should be considered in conjunction with newer NICE and other guidance on the clinical and cost-effectiveness of these agents.

4.5.3 Research priorities

One key flaw in the assembled clinical effectiveness evidence was the lack of long-term follow-up. We consider that the distinctiveness of the different stages of MS is open to question. Additionally, valuation of health benefits continues to be a vexing area for MS and this was an issue identified in the original guidance resulting from TA32. Additional priorities include:

- How and under what circumstances does MS progress through different types (CIS, RRMS, SPMS)? How do these transitions relate to changing imaging technologies and changes in clinical practice?
- Further research that does not concentrate on the lower end of the EDSS scale may be of value for populations with MS as survival and advances in support and aids for those with disabilities improve.
- The RSS was designed to collect longer-term observational data in this area, however a large-scale, longitudinal randomised trial comparing active first-line agents would contribute meaningfully towards resolving uncertainty about the remaining relative benefits of different IFN or GA formulations.
- We consider that a systematic review and meta-synthesis of qualitative studies relating to the lived experience of MS, with particular attention to the dominant clinical features, e.g. relapse and disability progression would be of value. This would provide a basis for an understanding of relevant health states and benefits that more closely matches the preferences and experiences of people living with the target condition.

5 BACKGROUND

5.1 *Introduction*

Multiple sclerosis (MS) is a progressive, degenerative disease affecting the central nervous system. It is characterised by inflammation and demyelination of the neurons, mediated by an autoimmune response by T-cells to white matter.

Although not yet fully understood, the aetiology of MS involves major genetic components[1] with two or more genes active in causing its development.[2, 3] There is also a body of literature linking the development of MS with environmental factors, or hypothesising the involvement of viral infections such as Epstein-Barr virus.[4-8]

Within the United Kingdom, prevalence is around 203/100,000 person-years, whilst incidence was 9.6/100,000 person-years between 1990 and 2010, with a female to male ratio of 2.4.[9] Peak incidence is at around 40 and 45 years of age (men and women, respectively) with peaks in prevalence at 56 and 59 years for men and women respectively.

5.2 *Types of MS*

The disease can develop and progress in three major forms: (i) relapsing remitting (RRMS); (ii) Primary progressive (PPMS); and (iii) Secondary progressive (SPMS);, of which RRMS originates from a single demyelinating event, known as clinically isolated syndrome (CIS).[10]

CIS events are isolated events of neurological disturbance lasting more than 24 hours, which indicate the first clinical demyelination of the central nervous system,[11] with clinical syndromes that are monofocal in nature (for example, optic neuritis and transverse myelitis) or multifocal (sucha s optical neuritis, limb weakness from transverse myelitis and cerebellar signs). Patients presenting with a clinical history of 1 attack are given a diagnosis of CIS. In these cases, MRI helps to confirm whether a diagnosis of MS can be given instead at the onset of symptoms. A diagnosis of MS requires that DIT and DIS criteria are fulfilled, and these can be checked using the MRI scan performed at onset of CIS. Patients with CIS who fulfil the DIS criteria, need evidence of DIT to become MS; and if DIT is not met at the baseline scan, it is necessary either to repeat the MRI scan to check whether there is a new lesion, or wait for a second clinical attack. Notably, then, delays in the onset to a second "relapse" for patients with CIS are equivalent to delays of MS progression

In 80% of cases, RRMS is the form of MS at time of diagnosis. In RRMS patients experience an exacerbation of symptoms followed by periods of remission. RRMS, as defined in research protocols, is characterised by episodes of relapses that last more than 24 to 48 hours. RRMS can be subtyped as rapidly evolving or highly active MS, and although these terms have not been precisely defined, they usually indicate two or more relapses within one year with evidence of increasing lesion frequency on MRI scans.[12] This classification is mainly used in reference to newer therapies like natalizumab and fingolimod.[13]

PPMS has an older age of onset, with greater susceptibility in men,[14] and is typically characterised by occasional plateaus in disease progression, with temporary minor improvements from onset.[15] Some PPMS patients experience relapses alongside disease progression.

SPMS follows on from RRMS but the disease course is progressive, with or without temporary relapses, remissions and plateaus in symptoms.[15] The transition is

The natural course of the disease is highly variable, with early stages of MS potentially developing into any of subtypes. However, each subtype is associated with cumulative neurological dysfunction, which is often measured using the Expanded Disability Status Scale (EDSS).[16] Transition from RRMS to SPMS occurs in 60% to 70% of patients initially diagnosed with RRMS, approximately 10 to 30 years from disease onset. About 15% of RRMS patients may be diagnosed with 'benign' MS, thus avoiding the progression of disability and conversion to SPMS.[17]

To date, there is no cure for MS. Currently approved drugs for MS act as immunomodulators or immunosuppressants with the aim of reducing the pathological inflammatory reactions and reducing the frequency and severity of relapses, and the rate of disease progression. Immunomodulation and immunosuppressing drugs used in MS are called disease-modifying therapies (DMTs).

5.3 *Disease modifying therapies*

5.3.1 Beta interferons

There are currently five licensed beta interferon (IFN-β) drugs in MS: two IFN β-1a (Avonex, Rebif), one pegylated IFN β-1a (Plegridy), and two IFN-β-1b (Betaferon, Extavia). These five drugs are recombinant forms of natural IFN-β, which is a 166 amino-acid glycoprotein which can be produced by most body cells in response to viral infection or other biologic inducers.[21] IFN β-1a are structurally indistinguishable from natural IFN-β whereas IFN β-1b are non-glycosylated forms that carry two structural changes compared to natural IFN-β (Met-1 deletion and Cys-17 to Ser mutation).

Depending on the formulation, the dose regimen is one intramuscular injection once a week (Avonex), one subcutaneous injection three times per week (Rebif), or one subcutaneous injection every other day (Betaferon, Extavia). The two IFN β-1b are the same drug (both are manufactured on the same production line). Pegylated IFN β-1a is a long-acting formulation of IFN β-1a obtained by adding methoxy-PEG-O-2-methylpropionaldehyde to IFN β-1a which allows less frequent administration (one subcutaneous injection every 2 weeks).

The precise mechanism of action of IFN-β in MS is not fully understood. The immunologic effects of IFN-β that are thought to have a potential action on MS are inhibition of T-cell co-stimulation/ activation processes, modulation of anti-inflammatory and pro-inflammatory cytokines, and decrease of aberrant T-cell migration.[22]

The main indication for IFN-β is the treatment of RRMS. For some patients IFN-β is indicated in response to a single demyelinating event with an active inflammatory process where there is determined to be a high risk of development of clinically definite MS. IFN β-1b is also licensed for use in SPMS, as is IFN β-1a SC 44μg three

times weekly (Rebif) in cases where SPMS remains with ongoing relapse activity. IFN-β drugs are not indicated for PPMS.

The most common reported adverse events of IFN-β are irritation at injection-site reactions and flu-like syndrome.[23] Other adverse events include pain, fatigue, headache and liver function abnormalities; a rare but important side effect is nephrotic syndrome. Adverse events may result in treatment discontinuation. Given the biological nature of recombinant IFN-β, patients are at risk of developing neutralising antibodies (NABs) against IFN-β. NABs are thought to increase relapse rates and the rate of disease progression.

Depending on the formulation, the current annual cost per patient of the beta interferons in the UK, assuming BNF list prices and considering a continuous treatment at standard dose, is between £7,264 and £10,572.[24]

5.3.2 Disease modifying therapies (glatiramer acetate)

There are two licensed formulations of glatiramer acetate (GA) (Copaxone). GA is the acetate salt of synthetic polypeptides, containing four naturally occurring amino acids. The mechanisms by which GA exerts its effects in patients with MS are not fully understood but it is now thought that GA induces a broad immunomodulatory effect that modifies immune processes which are currently believed to be responsible for the pathogenesis of MS.

According to the summary of product characteristics, GA is indicated for the treatment of RRMS, but not for PPMS or SPMS. The dose regimen is 20 mg daily (formulation of 20mg/mL) or 40 mg three times a week (formulation of 40mg/mL) by subcutaneous injection. The most common adverse events of GA are reaction of flushing, chest tightness, sweating, palpitations, headache and anxiety.[25] Injection-site reactions are observed in up to a half of patients.

The current annual cost per patient of GA in the UK, assuming BNF list prices and considering a continuous treatment at standard dose, can be estimated at £6,681-£6,704.[24]

5.3.3 Current use in the UK

IFN-β and GA are currently not recommended by NICE (Technology Appraisal 32, 'Beta interferon and glatiramer acetate for the treatment of multiple sclerosis', published January 2002) as they were considered not to be cost-effective. However, IFN-β and GA have been available in the NHS through a risk-sharing scheme, with the exception of one new brand of IFN-β-1b (Extavia) and of pegylated IFN-β-1a (Plegridy), which were released after the publication of TA 32. Within the risk-sharing scheme (RSS), a registry has been set up to record long term clinical outcomes of patients receiving IFN-β and GA. This review will consider the final data from this scheme alongside the clinical effectiveness evidence, and its implications for the clinical and cost-effectiveness of GA and IFN-β.

5.4 *Description of the health problem*

Multiple sclerosis (MS) is a neurodegenerative disorder characterized by inflammation and demyelination of neurons in the brain and spinal cord. It is a leading cause of non-traumatic disability in working-age adults, and

affects over 100,000 people in the UK. Although there is currently no cure for MS, there are a number of disease-modifying drugs available to help reduce the frequency of relapses and the rate of disease progression. IFN-β and GA are two such groups of drugs; at the time of the technology appraisal guidance 32 (2002), however, there was insufficient evidence of their clinical and cost-effectiveness. A risk-sharing scheme was put in place, allowing patients to access the drugs and the NHS to adjust prices based on cost effectiveness data, as well as monitor for long-term outcomes. This current study aims to appraise the clinical and cost-effectiveness of IFN-β and glatiramer, integrating evidence from the literature with data on long-term outcomes collected from the risk-sharing scheme. This introduction will summarize the pathogenesis, clinical course, epidemiology, and current service provision for MS.

5.4.1 Pathogenesis

Although the precise pathogenesis of MS is unclear, our current understanding is that it stems from auto-reactive inflammatory responses targeting the myelin sheaths of CNS neurons. This inflammatory response begins in the periphery with activation of T-helper cells that recognize CNS antigens. The subsequent inflammatory cascade leads and responds to disruption of the blood-brain barrier, allowing for increased transepithelial migration of activated immune cells, cytokines, and chemokines into the CNS. Once in the CNS, the autoimmune response leads to demyelination and axonal degeneration.

More recently, MS has been recognised as consisting of both neurodegenerative and inflammatory processes.[26, 27] Although neurodegeneration in MS is even less understood than inflammation, it is thought to be mediated by degeneration of transected axons, defects in ion balance, and loss of nutritional support to glial cells surrounding neurons.[28] Notably, investigations of autopsy specimens have shown that axonal loss can occur even in areas without acute inflammation, including in grey matter and normal-appearing white matter (NAWM).[29] These neurodegenerative processes are thought to be responsible for progressive and permanent disability.

5.4.2 Aetiology

A large body of evidence suggests a multifactorial aetiology of MS, with some interaction of genetic and environmental triggers causing the peripheral immune system to become activated against CNS antigens. Although the precise interaction remains unknown, a number of risk factors for MS have been identified.

Genetic

Unsurprisingly, genetic polymorphisms linked to MS have been identified primarily in immune response proteins. The first and most significant genetic locus was identified in the 1970s on the human leucocyte antigens (HLA) complex.[30, 31] HLAs encode part of the class II major histocompatibility complex (MHC) in humans, which presents processed foreign antigens to T cells for recognition.[31, 32] Variations within the HLA region have been consistently associated with a risk of MS, with the HLA-DRB1*15:01 allele particularly implicated[33-36]. It is also thought that the HLA complex carries genetic determinants of MS clinical progression.[31]

Although the HLA complex has the strongest and most long-standing linkage with MS, other genes are suspected of increasing disease susceptibility, age of onset and poorer prognoses for specific types of MS.[33] These genes

have been identified based on evidence from genetic linkage studies, microarray studies, and, more recently, genome-wide association studies (GWAS).[37] A seminal GWAS study performed by the International Multiple Sclerosis Consortium and the Wellcome Trust Case Control Consortium studied 465,434 single-nucleotide polymorphisms (SNPs) in 9,772 cases and 17,376 controls, implicating at least 59 non-HLA genes as associated with MS inheritance. These genes include those in cytokine, immune stimulation, and immunological signal transduction pathways.[33]

Despite substantial data on genetic risk for MS, the rate of concordance between monozygotic twins is modest at about 25%.[38] Additionally, a study reporting genome, epigenome, and RNA sequences in MS-discordant monozygotic twins was able to find no substantial difference accounting for MS-discordance. Such evidence points to the involvement of other causes in MS pathogenesis.[39]

Viral

Among all environmental risk factors investigated in MS aetiology, Epstein-Barr Virus infection has shown the strongest consistent evidence of association.[40] EBV was first suggested as a potential causative agent of MS because of the similarity in epidemiological distribution across age, geography, ethnicity, and socioeconomic status.[41] 99.5% of patients with MS test seropositive for EBV antibodies, compared to 94.2% of the general population.[42] The current evidence for EBV's role in MS is multifaceted: prospective studies note increased serum anti-EBV antibody titres before onset of MS;[43] a meta-analysis found that for both adults and children testing negative for EBV, the OR for developing MS was 0.18 (for adults, 95% CI [0.13, 0.26]) compared to people who tested positive;[44] and at the molecular level, EBV can be isolated from B-cell infiltrates in meninges.[45] Although EBV is a demonstrated risk factor for MS, its role in causation remains unproven.

Other environmental risk factors

Populations living farther from the equator, both native and foreign-born, have consistently shown increased MS risk[46-50].[51] In one meta-analysis, this correlation persisted even after adjusting for regional differences in genetic HLA-DRB1 alleles,[51] though it was not replicated in a separate meta-analysis using incidence instead of prevalence.[52] One hypothesis is that this effect is mediated by sun exposure and vitamin D levels, with one supporting meta-analysis of 11 studies finding lower mean serum 25(OH)D levels in patients with MS [46-50].[53] Other possible explanations include confounding by socioeconomic factors or the 'hygiene hypothesis'. Smoking is also implicated as a modest but consistent risk factor for MS, with smoking cessation suggested as an effective public health intervention that carries numerous other benefits.[40]

5.4.3 Presentation

Clinical symptoms

Although the initial signs of MS are variable between patients, they classically present with focal neurological symptoms and signs of CNS dysfunction around the third decade of life. Relapses may present as painful loss of vision in one eye (optic neuritis), unilateral motor or sensory disturbance (cortico-bulbar/spinal tract

involvement), double vision/vertigo/unsteadiness (brainstem or cerebellar syndrome), Lhermitte's phenomenon (pain down the spine/body on flexing the neck, from a cervical cord lesion), or bilateral leg and bladder dysfunction (spinal cord syndrome). Fatigue is a common but non-specific symptom. As MS progresses in severity, it can also lead to cognitive decline as well as changes in mobility, bladder/bowel function, and sexual function.

Imaging features

MRI modalities have an advantage over other imaging techniques with the ability to dampen resonance signals from the cerebrospinal fluid and intensify signals from sites of inflammation.[54] In sites of active inflammation, disruption of the blood-brain barrier allows lesions to be enhanced' with the administration (and take-up) of contrast, while chronic lesions are generally non-enhancing. MRI formally joined the diagnostic criteria for MS in 2001, and has rapidly become a primary tool for characterizing MS severity and progression. The characteristic MRI lesion is a cerebral or spinal plaque with high T2 signal, representing a region of demyelination with axon preservation. In the brain, plaques representing perivenular inflammation (and potential blood-brain barrier disruption) are known as 'Dawson's Fingers', and they are seen inthe periventricular regions radiating perpendicularly away from ventricles. Outside the periventricular region, plaques are also commonly found in the corpus callosum, sub/juxta-cortical region, optic nerves, and visual pathway.[55] Spinal cord lesions are nearly as common, though they more likely to be noticed clinically before MRI identification.

Pathology

Early acute stage lesions are active plaques characterised by breakdown of myelin, which may appear oedematous and inflamed histologically. Sub-acute stage lesions appear paler in colour and have higher focal regions of macrophages. Chronic stage lesions are inactive plaques with low activity of myelin breakdown, but characterised by gliosis, leading to the production of scar tissue.[56-58] Within the chronic stages of the lesions, attempts at remyelination occur but the process may be hampered and unsuccessful due to the scar tissue formed by gliosis.[59, 60]

5.5 *Diagnostic Criteria*

The diagnosis of MS is a clinical one, with supportive roles for neuroimaging and paraclinical findings. The fundamental requirement is for demonstrated CNS lesions disseminated in time and space (DIT and DIS, respectively). Initially this demonstration was purely based on clinical findings and history; over time, laboratory results (such as CSF oligoclonal bands) and paraclinical evidence (such as neuroimaging) have been included as possible bases of diagnosis.[61]

The McDonald criteria, newly revised in 2010,[62] continue to form the standard diagnostic tool for investigating suspected MS in research settings and, to a more flexible degree, in clinical practice.[63] An MS attack, relapse, or episode is defined by 'patient-reported symptoms or objectively observed signs typical of an acute inflammatory

demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection'.

The most 'secure' diagnoses are supported by 2+ MS attacks, with objective clinical evidence of at least 1 lesion and 'reasonable historical evidence' of the second. Patients who have had 2+ attacks with associated clinical signs of 2 or more separate lesions in the CNS are said to have clinically definite MS (CDMS). If objective clinical evidence for only 1 lesion is found, evidence for DIS can come from T2 lesions on MRI if they occur in at least 2 of 4 locations characteristic for MS (juxtacortical, periventricular, infratentorial, spinal cord). Evidence for DIT can be provided by new T2 or contrast-enhancing lesions on MRI appearing after disease onset, or the simultaneous presence of contrast-enhancing (active) and non-enhancing (chronic) lesions on the scan performed at onset of CIS. Patients presenting with a clinical history of 1 attack and objective clinical evidence of 1 lesion, but without sufficient evidence of either DIS or DIT, are diagnosed with CIS.

5.5.1 Recent trends in the McDonald diagnostic criteria

The Poser et al. criteria for MS diagnosis were published in 1983, and included two major categories of 'definite' or 'probable' MS, each with subgroups of 'clinical' or 'laboratory-supported'.[64] Diagnosis was made based on number of attacks, and lesions with clinical evidence, paraclinical evidence, and laboratory evidence. CIS or 'possible MS' was not included in the criteria, as those patients were not yet involved in research studies. The McDonald 2001 diagnostic criteria did away with the previous categories and instead focused on evidence for DIT and DIS. For the first time, it also explicitly allowed for MRI data to serve as evidence for DIS and DIT. Originally, demonstration of DIS meant meeting the Barkhol/Tintoré criteria[65] (or showing 2 MRI lesions and positive CSF), and demonstration of DIT could only be done by enhancing lesions appearing 3 months after a clinical event. With a 2005 revision to the criteria, DIT could also be demonstrated by appearance of new T2 lesions 1 month after a 'reference scan' (which was required to be 3 months post clinical onset).[66]

The McDonald 2010 revision further simplified previous diagnostic criteria. It allowed for lesions at 2 of 4 areas to provide evidence of DIS, as opposed to the previous Barkhol/Tintoré criteria.[65] It also simplified the DIT criteria by removing the requirement that the baseline MRI be at least 30 days post clinical event, and allowing for presence of simultaneous enhancing and non-enhancing lesions on the scan at onset of CIS to serve for DIT. After this revision, a diagnosis of MS could be confirmed based on just a single MRI (with enhancing and non-enhancing lesions disseminated in space). Because more patients meet the DIS and DIT criteria under the 2010 revision as opposed to the original guidelines or 2005 revision, more recently diagnosed patients are more likely to have a diagnosis of confirmed MS instead of CIS.

5.6 *Prognosis*

5.6.1 Disability as part of prognosis

Quantification of disability in multiple sclerosis has been used extensively to standardise characterizations of functional disease progression. The three Kurtzke scales have commonly been used to describe MS progression.

First, the functional systems scale is comprised of measures of functionality in 8 pre-chosen systems[16]; second, the Disability Status Score (DSS) is an eleven-point scale measuring global disability[71]; and third, the Expanded Disability Status Score (EDSS) is a modification of DSS measuring 20 points of disability.[72] The EDSS is currently used as the standard to measure disease progression in MS.

The EDSS quantifies disability in eight functional systems, specifically focusing on pyramidal, cerebellar, brain stem, sensory, bowel & bladder, visual, and cerebral/mental function (Scoring is detailed in Appendix 2).[16] An EDSS score of 0.0 would indicate normal neurology with no impairment in any system; an EDSS score of 4 suggests full ambulation without aid despite relatively severe disability; a score of 6 suggests needing unilateral support (ex. cane, crutch) to walk 100m; and a score of 7 suggests wheelchair confinement, with inability to walk >5m with support.[16]

5.6.2 Prognoses for disease progression

Prognostic data is primarily taken from longitudinal cohort studies, many of which can patients both on and off treatment. Patients who present with CIS have a 60-80% risk of developing clinically definite MS within 10 years if they have MRI lesions at the time of presentation, and ~20% risk if they do not (note that this prognosis will likely change with the revised McDonald 2010 diagnostic criteria for CIS) (reviewed in [73]). RRMS is thought to last for around 2 decades before transition to SPMS.[74] Up to 15% of patients with RRMS may be retrospectively diagnosed with 'benign' MS.[17] There is significantly less consensus about the natural history of disability in the progressive phase of MS, with median times to EDSS 6 ranging from 15-32 years.[74] Very generally, progression to EDSS 4 is suspected to occur after 1 decade, EDSS 6 after 2 decades, and EDSS 7 after 3 decades.[75, 76] Median ages for EDSS 4, 6, and 7 were 42, 53, and 63, respectively, for a cohort study of 1844 patients in Lyon.[77]

Risk factors for disease progression

MS is notoriously heterogeneous, and even when all known risk factors are combined, they provide only moderate prognostic value. Generally, observational data have found male gender, older age of onset, progressive state at onset, and higher number of MRI lesions to be predictive of a poor prognosis with faster disability progression.[78, 79] A recent systematic review has identified several key factors related to relapse frequency and recovery.[79] Relapse activity appears to decrease with age and disease duration, and cohort studies suggest that women experience relapses more frequently. Modifiable risk factors, including smoking, exposure to infectious disease and discontinuation of DMTs, also are associated with increased relapse frequency.

Relapse rates

There is some controversy over whether increased rates of relapse events represent an independent risk for disability progression in MS. Short-term studies suggest that relapses do not entirely regress, so that when EDSS scores are eleveated during relapses pateints do not return to their previous baseline.[80] Authors of these studies would conclude that a greater number of relapses, then, would lead to earlier increases in EDSS scores. Longer cohort studies, however, have noted that number of relapses is not associated with time to SPMS or EDSS 6.[75, 81] A study examining placebo groups from two large phase III trials also noted that half of patients satisfying criteria for 'confirmed progression' (definitions ranging from 1.0 EDSS increase for 3 months, to 2.0 EDSS increase for

6 months) were erroneously diagnosed, as their EDSS scores did not sustain progression even through the end of the trial.[82] Thus, in short-term studies, EDSS scores measured months after relapse may still be reflecting changes of active, not progressive, disease. These longer time scales for recovery from relapse may need greater recognition.

Most recently, a longitudinal cohort study by Leray et al. suggested that MS may be characterized by 2 distinct phases, with Phase 1 lasting from diagnosis until irreversible EDSS 3, and Phase 2 from EDSS 3 until EDSS 6. Notably, disability progression in Phase 1 did not influence Phase 2, and, similarly to previous studies, increased relapse during the first 2 years of MS only influenced time in Phase 1. Relapses after EDSS 3 were not associated with continued disability progression. Previously-characterized risk factors of gender, age of onset, and relapse history were not related to disability progression in phase 2.[83] These data are in line with previous studies suggesting that while rates of relapse early in disease predicts disease progression, relapses later in RRMS or during SPMS may not significantly predict or influence disability progression.[84, 85]

Prognoses for mortality

Patients with MS have an average lifespan 7-14 years shorter than matched controls.[86] A meta-analysis of standardized mortality rates (SMR) found that patients overall had a 2.81 SMR compared to controls, which suggests 181% more mortality per year than anticipated at any age.[87] This was especially increased for those with EDSS>7.5, who, in a separate study, were found to have a 4.0 SMR compared to controls.[88] One review notes that in most cohort studies of people with MS, MS is cited as a cause of between half and three-quarters of deaths. It also notes wide variation in the proportion of deaths ascribed to MS, resulting from variations in assessment, interpretation, and coding practices. In particular, death from suicide is inconsistently reported as MS-related, though there is a substantially increased risk of suicide among people with MS. [86]

5.6.3 Epidemiology

Prevalence and incidence

An international survey including data from 92 countries estimated the median global prevalence of MS to be 33/100,000, or about 2.3 million people worldwide.[63] This prevalence has been increasing in the past few decades, primarily because of increased survival and diagnosis, but a meta-regression analysis suggested that there is also likely a true increase in MS incidence.[52] This analysis also suggested that the increase is primarily in women, who already face double the burden of MS compared to men.[52, 89-92 93]

A recent systematic review reported estimates for MS prevalence in the UK ranging from 97.26 in England in 1998[94] to 230.60 per 100,000 in Scotland in 2008.[89, 95] Incidence estimates were less common, and ranged from 4.4 to 12.2 per 100,000 person-years.[89] Analysis of the UK General Practice Research Database between 1990-2010[9], similarly, showed an estimated prevalence of 258.5/100,000 women and 113.1/100,000 men, with incidence of 11.52/100,000 women per year and 4.84/100,000 men per year. Incidences peaked in women of age 40 and men of age 45. Although no systematic reviews of longitudinal incidence trends specifically look at the UK, the analysis of the UK GPRD estimates that while overall prevalence of MS is increasing due to increased survival, incidence has decreased by 1.5% per year (though this may be due to decreased false positive

diagnoses). This analysis estimates that 126,669 people with MS were living in the UK in 2010, though the number may be inflated about 20% with inaccurate diagnoses.[96]

Burdens of disease.

The effects of MS have major ramifications for the patient and carers, as well as financial implications for the patient and the state.

Disability

MS has a wide range of effects, ranging from mobility problems to bladder/bowel dysfunction, sexual dysfunction, fatigue, visual disturbances, pain, depression, and memory changes.[97] Interviews with 301 patients in Wales found that weakness, sensory changes, and ataxia were the most commonly-reported symptoms of MS,[98] while a postal survey of 223 unrepresentative MS patients found fatigue, bladder/bowel problems, balance problems, and muscle weakness to be the 'worst' symptoms.[97, 99] In terms of functional impacts, mobility, ability to use stairs, and outdoor transport were cited as the most significantly impacted by disease, whereas activities like dressing and feeding were more preserved.[100] Surveys of mobility in randomly-sampled populations of patients with MS note that slightly less than half (41.4%-53%) require walking aids or a wheelchair (EDSS 6+).[100-102]

Quality of life

A survey based on the EuroQoL 5 dimensions questionnaire (EQ-5D) suggested that 82.5% of 4516 patients had experienced difficulty in their daily activities, and 76% experienced pain and problems with mobility, with patients rating their mean health state as 5.97 out of 10[103] (cf. UK general population 8.3[104]). Another study with 2708 participants living with MS established a mean utility of 0.49 (perfect health equal to 1.00), with an inverse relationship between EDSS score and quality of life.[105] The study established that quality of life was affected by type of disease, recent relapse and length of time since diagnosis, with SPMS demonstrating lowest quality of life across subtypes.

The lifetime prevalence of depression patients with MS is ~50%, with an estimated annual prevalence of 20%.[106] Meta-analysis showed a 2.13 SMR for suicide compared to the general population,[87] though accuracy is difficult to assess because reporting of suicide as a cause of death continues to be heavily influenced by cultural biases.[86] Risk factors for suicide in patients with MS may include depression, social isolation, younger age, advanced disease subtype, low socio-economic status and higher EDSS score.[107]

Cost

A number of cost estimates for MS exist, most of them based on cost-of-illness analyses (which are contested)[108] with significant variation in methodologies and costs accounted for.[97] Most recently, analyses estimated an average of between £30,460 - £39,500 per person-year.[109, 110] Overall indirect costs, including those from lost employment, are projected to be greater than direct costs of care, and costs are greater for those in later stages of disease.[97] Estimated cost of relapse range from £519[111] to £2115,[112] depending on level of care required.

Cross-sectional surveys of disability in patients with MS demonstrate substantial changes to employment. Surveys with an average age of 50 have noted that most patients are not working,[100, 113] and most early or partial

retirement is due to MS.[102, 113] In a study of 301 patients in England in the 1980s, 27% of patients report decreased standard of living because of employment changes and care costs, and 36% of carers interviewed also had their careers impacted.[113] Lost employment is estimated to currently account for 34%-40% of the total cost of MS.[109, 110]

Patient expectations and perceptions of disease

The literature describing qualitative experiences of patients is not as comprehensive as that surrounding pharmacological treatments and pathology of MS. Collectively, however, what does exist unsurprisingly describes the experience of symptom onset and diagnosis as a negative one.[114-116] Patients inevitably experience distress and anxiety as they become aware of symptoms[116], and this can continue or be amplified as they learn of their diagnosis; the diagnosis can, however, also be a source of relief because it provides an explanation for symptoms.[115] Receiving adequate information from healthcare professionals at the time of diagnosis can have a positive effect on patients' wellbeing and self-identification of relevant support services,[115] while a lack of information or empathy can be linked to frustration, anxiety, and fear.[116] The transition from RRMS to SPMS is also a challenging time for patients, as this requires adjusting to new 'realities' and preparing for forthcoming challenges in a declining trajectory.[117] A recent qualitative systematic review emphasizes the importance of support from healthcare providers, and an accessible healthcare system.[118] Comprehensive care plans including patient and carer support alongside therapeutics are described as key for successful management of MS.[119]

Current service provision

At present there is no cure for MS, but treatment options exist based on the stage and subtype of disease. Currently approved drugs for MS act as immunomodulators or immunosuppressants, with the aim of reducing the pathological inflammatory reactions occurring in MS, and thus the frequency and severity of relapses and the rate of disease progression.[120] Management of MS also includes non-pharmacological options such as lifestyle adjustments and rehabilitation, which are also included in the NICE guidelines for MS management.[19]

Treatments to reduce the risk of relapses

Drugs aimed at reducing the risk of relapses are called disease-modifying therapies (DMTs). In addition to the DMTs introduced in section 5.3, several newer drugs are licenced for use in the UK. Five newer drugs are recommended by NICE for the treatment of MS: natalizumab, teriflunomide, alemtuzumab, fingolimod and dimethyl fumarate. A summary of these recommendations is provided in Table 1. DMTs are indicated in the treatment of classic RRMS, with the exception of natalizumab and fingolimod, which are recommended only in patients with highly active RRMS. Among DMTs, interferon beta-type drugs and GA are indicated for patients with CIS.

Immunosuppressive agents, such as azathioprine, cyclophosphamide, mitoxantrone, and methotrexate, can also be used in the management of MS. These agents can provide potential benefit through downregulating pathogenic mediators of MS, but can also induce severe adverse effects on the immune system. Consequently, those drugs are only indicated in patients with aggressive forms of MS, including patients who experience very frequent and

severe relapses. They are not included in any NICE guidelines currently, though they continue to be used for MS[121] and a systematic review suggests their effectiveness in preventing relapse recurrence.[122]

Table 1: NICE technology appraisal guidelines and recommendations for DMTs

Treatment	Technology appraisal	NICE recommendation
Alemtuzumab	TA312, 05/2014	recommended as an option, within its marketing authorisation, for treating adults with active RRMS
Dimethyl fumarate*	TA320, 08/2014	recommended as an option for treating adults with active RRMS, only if they do not have highly active or RES RRMS
Fingolimod*	TA254, 04/2012	recommended as an option for the treatment of highly active RRMS in adults, only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon
Natalizumab	TA127, 08/2007	recommended as an option for the treatment only of rapidly evolving severe RRMS (RES)
Teriflunomide*	TA303, 01/2014	recommended as an option for treating adults with active RRMS only if they do not have highly active or RES RRMS

Active RRMS: defined as 2 clinically significant relapses in the previous 2 years
RES RRMS: rapidly evolving severe RRMS, defined by two or more disabling relapses in 1 year, and one or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.
*available with discount agreed to by manufacturer in a patient access scheme

Treatment of acute relapses

Steroids are commonly used and recommended to treat acute relapses. Steroids are aimed at reducing duration of relapses by shutting down production of inflammatory cytokines and destroying activated lymphocytes that cause demyelination; these drugs are not, however, thought to induce long-term benefit in the course of the disease.[123] NICE guidelines[124] recommend use of oral methylprednisolone 0.5g daily for 5 days in the first instance and to consider intravenous methylprednisone 1g daily for 3-5 days as an alternative if oral steroids are not tolerated or have failed, or if hospital admission for severe relapse or monitoring is required. Patients should not be offered a supply of steroids to administer at home for prophylactic use for future relapses. Lastly, patient education should target management of potential complications, such as mental health changes or irregularities in blood glucose. NICE guidelines[124]

Pharmacological treatment of symptoms

Current NICE guidelines offer advice to healthcare professionals, patients and families on the management of MS symptoms.[19] Recommendations include amantadine use for fatigue (though it does not have marketing authorisation in this indication), and baclofen or gabapentin for spasticity, with combinations of baclofen and gabapentin possible if individual drugs cannot reach a dosage for adequate relief.[124] Other drugs such as tizanidine, dantrolene, or benzodiazepines should be considered as second or third-line options. NICE guideines also noted that fampridine, recently approved in Europe to improve walking ability in people with MS, has not been recommended by NICE as a cost effective treatment. A systematic review, however, concluded that the absolute

and comparative efficacy and tolerability of anti-spasticity agents in MS was poorly documented, and no recommendations could be made to guide prescription.[125]

For treatment of psychological changes, rivastigmine, donepezil and memantine, which are classically used in Alzheimer's disease, have been tested to improve cognitive impairment, but overall evidence for their efficacy in MS patients has proved inconclusive.[126] The treatment of depression includes consideration of both psychotherapy and antidepressant medication. Commonly used medications are selective serotonin reuptake inhibitors such as fluoxetine, paroxetine and sertraline. A recent systematic review showed that depression severity was improved in three pharmacological studies of depression treatment in MS.[127] NICE guidelines state that amitriptyline can be considered to treat emotional liability.

Managing disability

Non-pharmacological treatment options are directed towards a rehabilitative approach with specialist assistance from a multidisciplinary team.

There is evidence that physical activity alone can improve fatigue, and it has been linked to improvement in aerobic capacity, gait parameters and QoL[128, 129]. Suggestions for an effective rehabilitation regime include progression of physical activity from basic to integrated functions,[130] to utilize working muscles while avoiding muscle overload. Although RCTs have shown some evidence of improved mobility and QoL from exercise interventions, however, systematic reviews have not reached consensus on whether the studies – which are especially limited by small samples and risk of bias from lack of blinding – are enough to make guided exercise prescriptions.[131-133] Urinary incontinence affects approximately 75% of patients and can substantially impact quality of life.[134] NICE guidelines on lower urinary tract dysfunction in neurological disease are available, and should be used to inform treatment.[135]

Care should also be taken in the management of mental health of patients. Interventions should be aimed at regular monitoring of any depressive states and mental health services should be offered routinely to encourage participation.[136] Education for all healthcare providers and the patient in coping mechanisms may help improve QoL.[137]

6 DESCRIPTION OF TECHNOLOGY UNDER ASSESSMENT

In accordance with the NICE scope, this MTA focuses on IFN-β (including pegylated IFN β-1a) and glatiramer acetate.

6.1 *Beta interferons (IFN-β)*

Interferons (IFNs) are proteins that bind to cell surface receptors, initiating a cascade of signaling pathways ending with the secretion of antiviral, antiproliferative, and immunomodulatory gene products.[138] Natural IFN-β is a 166 amino-acid glycoprotein that can be produced by most cells in response to viral infection or other biologic inducers.[21] There are two types of recombinant IFN-β, known as IFN β-1a and IFN β-1b. IFN β-1a is a glycosylated form structurally undistinguishable from natural IFN-β;[21] recombinant IFN β-1b is a non-glycosylated form that carries one amino- acid substitution.[139]. Several in-vitro studies have concluded that biologic activity of some IFN-β-1a formulations is greater than that of IFN β-1b [21, 139, 140] but the clinical implications of such differences are unknown. Furthermore, those studies have not compared all the approved formulations of recombinant IFN β.

The precise mechanism of action of IFN-β in MS is not fully understood, but some potential actions include inhibition of T-cell activation, modulation of inflammatory cytokines, and decrease of aberrant T-cell migration into the CNS. [22]

There are currently five licensed IFN-β: two IFN β-1a (Avonex, Rebif), one pegylated IFN β-1a (Plegridy), and two IFN β-1b (Betaferon, Extavia):

- One formulation of IFN β-1a (Avonex) is given at the recommended dosage of 30 µg (6 million IU), administered by intramuscular injection once a week.
- The other formulation of IFN β-1a (Rebif) is given at the recommended posology of 22 µg (6 million IU) or 44 micrograms (12 million IU) three times per week by subcutaneous injection.
- IFN β-1b (Betaferon, Extavia) is given at the recommended posology of 250 µg every other day by subcutaneous injection.
- Pegylated IFN β-1a (Plegridy) has polyethylene glycol (PEG) added to the N-terminus of IFN β-1a, allowing for less frequent administration. Its recommended dosage is 125 µg injected subcutaneously every 2 weeks.

The current licensed indications of IFN-β are listed in Table 2. Their main indication is for treatment of patients with relapsing-remitting MS (RRMS); most (Avonex, Rebif, Betaferon/Extavia) also have indications indicated in patients with a single demyelinating event with an active inflammatory process and at high-risk of developing CDMS. IFN β-1b is licenced for use in patients with secondary progressive MS (SPMS). IFN β-1a (Rebif) is licensed with SPMS with ongoing relapse activity. IFN-β are not indicated for primary progressive MS (PPMS).

The most commonly reported adverse events of IFN-β are injection-site reactions (mainly inflammation) and flu-like syndrome (including fever, chills and myalgias, and headache) but these generally decline markedly after the first year of treatment.[23] Other adverse events include hypersensitivity reactions, blood disorders (mainly

leucopenia), menstrual disorders, mood and personality changes. Adverse events may be responsible for treatment discontinuation.

Because of its biological nature, recombinant IFN-β also carries a risk for patients of developing neutralizing antibodies (NABs),[141] and this is thought to reduce the treatment efficacy.[142] The occurrence of NABs depends on patient-specific factors but also treatment-specific factors like formulation, route of administration, dosage, and frequency of administration. Given their different natures and routes of administration, the immunogenicity of IFN-β varies among the formulations of IFN-β. A recently published systematic review of randomised trials showed that the rate of patients developing NABs was 2.0%-18.9% for Avonex, 16.5%–35.4% for Rebif, and 27.3%–53.3% for Betaferon.[143] Some guidelines recommend testing patients treated with IFN-β for the presence of NABs after 12 and 24 months of treatment.[141, 144]. In the UK, the monitoring of NABs is not performed in routine practice.

According to net prices listed in the British National Formulary, the current annual cost per patient of beta interferons in the UK can be estimated at £8,502 for Avonex, £7,976/ £10,572 for lower dose/higher doses of Rebif, and £7,264 for Betaferon/Extavia. Estimated costs in 2013-14 for IFN-β in England were £52,000,000 with 27.6% growth from 2012-13.[145].

As of July 2016, no biosimilar version of IFN-β is available in the UK.

6.2 *Glatiramer acetate (GA)*

Glatiramer acetate is a synthetic molecule containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine and L-lysine. It was initially created to mimic myelin basic protein (MBP), a suspected autoimmune antigen, and induce a mouse form of MS. Surprisingly, it prevented MS induction in mice, triggering clinical studies of glatiramer as a treatment for MS.[138] It is now thought that glatiramer induces a broad immunomodulatory effect, with actions including competition for the binding of antigen presenting cells; antagonism at specific T-cell receptors; and promotion of anti-inflammatory responses in dendritic cells, monocytes, and B-cells.[146]

Two formulations of GA are currently used: 20mg/mL and 40mg/mL (Copaxone, TEVA UK), equivalent to 18 mg or 36 of glatiramer base respectively. The dose regimen is 20 mg daily (formulation of 20mg/mL) or 40 mg three times a week (formulation of 40mg/mL) by subcutaneous injection. See Table 2. As of February 2016, no generic version of Copaxone is available in the UK.

GA is indicated for the treatment of patients with RRMS. It is not indicated for PPMS or SPMS. The most common adverse events of glatiramer are flushing, chest tightness, sweating, palpitations and anxiety,[25] and injection site reactions are observed in up to a half of patients.

The current annual cost per patient of glatiramer acetate in the UK can be estimated at £6,681-£6,704.[145] Generic prices are not yet available.

Table 2: Licensed indications for interferon beta and glatiramer acetate (as reflected in the NICE scope)

Brand name	INN	Recommended Usage	Indications
Avonex	IFN β-1a	Dose: 30 µg (6 million IU) Administration: intramuscular injection Frequency: once a week	• RRMS. In clinical trials, this was characterised by two or more acute exacerbations (relapses) in the previous three years without evidence of continuous progression between relapses. • Patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis. • Should be discontinued in patients who develop progressive MS.
Rebif	IFN β-1a	Dose: 22 µg (6 million IU) or 44 µg (12 million IU) Administration: subcutaneous injection. Frequency: Three times weekly	• RRMS. In clinical trials, this was characterised by two or more relapses in the previous two years. • Patients with a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis. • Efficacy has not been demonstrated in patients with SPMS without ongoing relapse activity
Betaferon Extavia	IFN β-1b	Dose: 250 µg (8 million-IU) Administration: subcutaneous injection. Frequency: every other day	• Patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing CDMS • Patients with RRMS and two or more relapses within the last two years. • Patients with SPMS with active disease, evidenced by relapses.
Plegridy	Pegylated IFN β-1a	Dose: 125 µg Administration: subcutaneous injection: Frequency: every 2 weeks	• Adult patients for the treatment of RRMS
Copaxone	Glatiramer acetate (GA)	Dose: 20mg or 40mg Administration: subcutaneous injection. Frequency: daily (20 mg) or three times weekly (40 mg)	• Treatment of relapsing forms of multiple sclerosis (MS). It is not indicated in primary or secondary progressive MS. • Glatiramer acetate in the 20 mg formulation has been studied in both RRMS and CIS.

6.3 *Care pathways for IFN- β and GA*

IFN-β and GA are considered first-line treatments for RRMS, except for patients with highly active RRMS, in which more advanced treatments (e.g. natalizumab) are considered most appropriate. Though some patients prefer dimethyl fumarate or teriflunomide because of their oral mode of administration, IFN-β and GA both have well-established long-term safety profiles that avoid some of the more severe side effects presented by other drugs, e.g. the rare but serious complications of progressive multifocal leukoencephalopathy associated with the reactivation of the John Cunningham virus (JCV) in dimethyl fumarate. Additionally, some patients may choose not to take IFN-β or GA, especially after CIS, or if the course of MS appears to be benign. Patients receive specialist advice, including from neurologists and nurses specialist in MS care, in choosing which DMT to initiate. It is common for MS patients to see a neurologist about once a year for maintenance, and MRIs are administered generally not more than once a year. Exacerbations may be managed by local GPs or by specialist neurology services depending on severity and complexity.

Switching between first-line treatments mainly occurs because of side effects. Patients may escalate to a second-line treatment if MS is highly active, i.e. characterised by multiple disabling relapses in a year, or unchanged relapse rate during first-line treatment.

Upon transition to SPMS—a diagnosis which is made retrospectively—patients are supposed to cease use of drugs that are not licenced for SPMS. However, there is anecdotal evidence that patients may continue on these drugs because of perceived benefits for relapse rate and the absence of any other treatment for SPMS.

6.4 *The UK Multiple Sclerosis Risk Sharing Scheme*

The last technology appraisal for beta interferons and glatiramer in the treatment of MS (TA32) did not find sufficient evidence of clinical and cost-effectiveness to recommend treatment.[147] The Department of Health set up a risk-sharing scheme (RSS) to provide the then-licenced formulations of interferon β-1a (Avonex, Rebif), interferon β-1b (Rebif) and glatiramer (Copaxone) to patients.[148] Under this arrangement, the benefit of each drug would be regularly assessed using target outcomes agreed upon with manufacturers. Price for each drug would be scaled, as necessary, to reach a target level of cost-effectiveness, set at the start of the scheme as £36,000/quality-adjusted life-year (QALY). As part of the RSS, patients meeting the criteria for treatment were enrolled in a cohort and monitored regularly for evidence of disability progression and treatment benefit. Analysis of the six-year data of this clinical cohort[149] compared disease progression against a historical comparator and suggested that, on the whole, the DMTs included in the RSS reduced disability progression and did so to the agreed level of cost-effectiveness.

Because all patients in the RSS received treatment, a comparator cohort including patients with measurement of disease progression without access to DMTs was needed. Several natural history cohorts meeting these criteria exist. The six-year interim analyses used the British Columbia cohort, which was initiated in 1980, before DMTs were made routinely available in Canada. The cohort has prospectively recorded EDSS scores and covers about 80% of the relevant MS population in that area, providing a rich source of data about the natural history of MS.[150,

[151] Patients from the British Columbia cohort who would have met the criteria for prescribing interferon or glatiramer were selected for comparison to those in the UK risk-sharing scheme.[149, 151, 152]

7 DEFINITION OF THE DECISION PROBLEM

7.1 *Decision problem and aim*

To appraise the clinical and cost-effectiveness of beta interferons and glatiramer acetate within their marketing authorisation for treating multiple sclerosis, as an update to technology Technology Appraisal guidance 32.

In this assessment, we will appraise beta interferon and glatiramer acetate using published data and taking account of additional data on long-term outcomes from the risk sharing scheme.

As requested by NICE, we have included beta interferons and glatiramer acetate to be compared with best supportive care. NICE commented that, 'Since Technology Appraisal 32 was published another interferon 1b (Extavia, Novartis), a pegylated interferon beta 1a (Plegridy, Biogen Idec) and a new formulation of glatiramer acetate (Copaxone, Teva pharmaceuticals) have been granted marketing authorisations. These technologies were not included in the risk sharing scheme because they were not appraised in Technology Appraisal 32. It has been determined by NICE that it is relevant to include these technologies in this appraisal so that guidance can be issued for all beta interferons and formulations of glatiramer acetate currently licensed for MS in the UK. Further active treatments that have been licensed and recommended by NICE (including teriflunomide, fingolimod, natalizumab, alemtuzumab and dimethyl fumerate) will not be considered in this appraisal.'

In addition, people with CIS will be considered in this appraisal.

7.2 *Objectives*

Our objectives were: a) to systematically review the evidence for the clinical effectiveness of

- IFN β-1a;
- Pegylated IFN β-1a;
- IFN β-1b; and
- GA

in people with

- relapsing multiple sclerosis (including people with relapsing remitting multiple sclerosis and people with secondary progressive multiple sclerosis with active disease, evidenced by relapses), and
- clinically isolated syndrome, that is, a single demyelinating event, who are considered at high risk of developing subsequent multiple sclerosis;

against the following comparators:

- best supportive care without disease modifying treatment, and
- beta interferons and glatiramer acetate compared with each other;

and investigating the following outcomes:

- relapse rate;
- transition to clinically definite MS, in the case of CIS;
- severity of relapse;
- disability (for example, expanded disability status scale [EDSS]);
- symptoms of multiple sclerosis such as fatigue, cognition and visual disturbance;
- freedom from disease activity;
- discontinuation due to neutralising antibodies;
- mortality;
- adverse effects of treatment; and
- health-related quality of life;

and b) to systematically review existing economic evaluations, including use of the existing RSS model; to develop a *de novo* economic model for CIS; to assess the cost effectiveness of the treatments (IFN β-1a, pegylated IFN β-1a, IFN β-1b, and GA) in treatment of CIS and RRMS against the stated comparators, expressed in incremental costs per quality-adjusted life year, with a time horizon sufficiently long to reflect any differences in costs or outcomes between the technologies being compared and from an NHS and Personal Social Services perspective; and to update model parameters and inputs to reflect available evidence from the literature, current costs, the NICE reference case, current practice, and new data from the risk sharing scheme.

8 METHODS FOR ASSESSMENT OF CLINICAL EFFECTIVENESS

8.1 *Protocol registration*

We presented our protocol to a Stakeholder Information Meeting on 29 February 2016 and subsequently registered it on PROSPERO as CRD42016043278.

8.2 *Identification of studies*

Initial scoping searches were undertaken in MEDLINE and the Cochrane Library in October 2015 to assess the volume and type of literature relating to the assessment question and to inform further development of the search strategy. Several relevant systematic reviews from the Cochrane Database of Systematic Reviews were identified.[153-157]

The following search strategy was designed to capture randomised controlled trials (RCTs) of DMTs for patients with RRMS, SPMS or CIS. An iterative procedure was used to develop the planned searches with reference to previous systematic reviews.[153-158] Clinical searches were restricted to RCT evidence. The included and excluded study lists from previous relevant Cochrane systematic reviews were checked.[155, 156] The main database searches for multiple sclerosis were undertaken in January and February 2016 and limited by date to the beginning of 2012 (the year the searches were undertaken for the broad review and network meta-analysis (NMA) by Filippini, et al., 2013[156]) onwards. This review was chosen because of the breadth of its scope, search strategy and eligibility criteria. Other more recent reviews were considered to be more limited in terms of the types of MS covered and the types of studies included. An additional targeted search for RCTs in CIS, not limited by date, was performed. A full record of searches is provided in Appendix 1. These searches were developed for MEDLINE and adapted as appropriate for the other databases.

The search strategy comprised the following main sources:

- Searching of electronic bibliographic databases including trials in progress
- Scrutiny of references of included studies and relevant systematic reviews
- Contact with experts in the field
- Screening of websites for relevant publications

We ran electronic searches on the following databases:

- Cochrane Multiple Sclerosis and Rare Diseases of the CNS group specialized register
- MEDLINE (Ovid)
- MEDLINE In-Process & Other Non-Indexed Citations (Ovid)
- Embase (Ovid)
- Cochrane Library (Wiley), including Cochrane Database of Systematic Reviews, CENTRAL, DARE, NHS EED, and HTA databases
- Science Citation Index and Conference Proceedings - Science (Web of Science)
- UKCRN Portfolio Database

We also searched the trial registers at ClinicalTrials.gov and WHO ICTRP.

All bibliographic records identified through the electronic searches were collected in a managed reference database. The reference lists of included studies and relevant review articles were checked and the companies' websites were screened for relevant publications. The included studies and reference lists of company submissions were checked for relevant unpublished studies and any additional published studies. Other grey literature searches were undertaken using the online resources of the following organisations (see Table 3). More details of these website searches are provided in Appendix 1.

Table 3: Online resources searched for relevant literature

Companies	Bayer	http://www.bayer.co.uk/ http://pharma.bayer.com/
	Biogen Idec	https://www.biogen-international.com/ https://www.biogen.uk.com/
	Merck Serono	http://biopharma.merckgroup.com/en/index.html
	Novartis	https://www.novartis.com https://www.novartis.co.uk/
	Teva Pharmaceuticals	http://www.tevapharm.com/research_development/ http://www.tevauk.com/
Patient carer groups	Brain and Spine Foundation	http://www.brainandspine.org.uk
	Multiple Sclerosis National Therapy Centres	http://www.msntc.org.uk
	MS UK	http://www.ms-uk.org
	Multiple Sclerosis Society	https://www.mssociety.org.uk
	Multiple Sclerosis Trust	https://www.mstrust.org.uk
	Neurological Alliance	http://www.neural.org.uk
	The Brain Charity (formally known as Neurosupport)	http://www.thebraincharity.org.uk
	Sue Ryder	http://www.sueryder.org
Professional groups	Association of British Neurologists	http://www.theabn.org
	British Neuropathological Society	http://www.bns.org.uk
	Institute of Neurology	https://www.ucl.ac.uk/ion https://www.ucl.ac.uk/ion/departments/neuroinflammation http://discovery.ucl.ac.uk
	Primary Care Neurology Society	http://www.p-cns.org.uk
	Therapists in MS	https://www.mstrust.org.uk/health-professionals/professional-networks/therapists-ms-tims/research
	United Kingdom Multiple Sclerosis Specialist Nurse Association	http://www.ukmssna.org.uk
Research groups	Brain Research Trust	http://www.brt.org.uk/research
	British Neurological Research Trust	http://www.ukscf.org http://www.ukscf.org/about-us/bnrt.html
	Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System	http://www.cochranelibrary.com http://msrdcns.cochrane.org/our-reviews
	National Institute for Health Research	http://www.nihr.ac.uk/research/ http://www.nihr.ac.uk/industry/ http://www.nihr.ac.uk/policy-and-standards/

8.3 *Inclusion criteria*

We included studies that met the following criteria.

The **study design** was a randomised controlled trial, a systematic review, or a meta-analysis.

The **population** was people diagnosed with RRMS, SPMS, or CIS.

The **intervention** was one of the following drugs, when used within indication (see Table 2):

- IFN β-1a;
- Pegylated IFN β-1a;
- IFN β-1b; and
- GA.

We only included drugs when used within marketing authorisation, i.e. when the posology in the trial matched that in the indication, because of the extensive clinical use of these drugs and the corresponding safety and effectiveness profile of these established dosages. A wide variety of alternative dosages has been used across a variety of trials. It was judged that including dosages not matching the indication could present misleading estimates of effectiveness or safety and would introduce unnecessary heterogeneity.

The **comparator** was best supportive care without DMT, or another of the interventions when used within indication. In this review, best supportive care corresponded to arms of RCTs where patients received either placebo added to standard care or no treatment.

The reported **outcomes** included at least one of the following:

- Relapse rate;
- Progression to multiple sclerosis (for patients with CIS);
- Severity of relapse, defined as rate of steroid-treated relapses or rate of relapses graded as moderate or severe;
- Disability, including as measured by the Expanded Disability Status Scale;
- Multiple sclerosis symptoms, such as fatigue, cognition and visual disturbance;
- Freedom from disease activity, defined as composite clinical and MRI outcomes;
- Mortality;
- Health-related quality of life (HRQoL);
- Treatment-related adverse events;
- Discontinuation due to adverse events; and
- Discontinuation due to loss of effectiveness attributed to neutralising antibody formation. We did not consider the rate of neutralising antibody formation alone because of its limited clinical relevance in practice.

The study was reported as a full-text report in English.

8.4 *Exclusion criteria*

We excluded:

- Studies that compared an eligible intervention against an irrelevant comparator;
- Studies that examined an eligible intervention used with a non-recommended dose regimen;
- Studies reporting MRI outcomes alone;
- Studies reporting early versus late treatment only;
- Studies that only examined MS subtypes other than those in the eligible population;
- Studies that only examined patients with highly active or rapidly evolving MS, as best supportive care is not an appropriate comparator for these populations; and
- Studies reported as abstracts or conference proceedings, or reported not in the English language.

8.5 *Study selection process*

First, we examined relevant past systematic reviews (including Tramacere et al. 2015,[155] Filippini et al. 2013[156] and Clerico et al. 2008[154]) for studies meeting the inclusion criteria. We verified inclusion of these studies by examining their full text.

For updated and new searches (including for studies addressing CIS), we collected all retrieved records in a specialised database and duplicate records were identified and removed. The reviewers pilot-tested a screening form based on the predefined study inclusion and exclusion criteria. Subsequently, two reviewers (XA and GJMT) applied the inclusion/exclusion criteria and screened all identified bibliographic records for title/abstract (level I) and then for full text (level II). Any disagreements over eligibility were resolved through consensus or by a third party reviewer (AC). Reasons for exclusion of full text papers were documented. The study flow was documented using a PRISMA diagram.[159]

8.6 *Quality assessment strategy*

Systematic reviews used to locate primary studies were appraised using the AMSTAR checklist.[160] All primary studies were appraised using the Cochrane risk of bias assessment tool.[161] Appraisal was undertaken by two reviewers. Uncertainty and/or any disagreements were crosschecked with a second reviewer and were resolved by discussion.

8.7 *Data extraction strategy*

For all included studies, the relevant data were extracted independently by two reviewers using a data extraction form informed by the NHS Centre for Reviews and Dissemination (CRD).[162] Uncertainty and/or any disagreements were crosschecked with another reviewer and were resolved by discussion. The extracted data were entered into summary evidence tables (see Appendix 2 for a sample data extraction sheet). Where multiple arms

were presented of which only some were relevant to our analysis, we extracted data for only those arms. The extracted information included:

- study characteristics (i.e., author's name, country, design, study setting, sample size in each arm, funding source, duration of follow-up(s), and methodological features corresponding to the Cochrane risk of bias assessment tool);
- patient baseline characteristics (i.e., trial inclusion/exclusion criteria; number of participants enrolled, and number of participants analysed; age, race, and gender; disability (including as measured by EDSS) at baseline; time from diagnosis of MS to study entry; and relapse rate at baseline);
- treatment characteristics (e.g., type of drug, method of administration, dose, and frequency; drug indication as stated; definition of best supportive care as described by trialists); and
- outcome characteristics for each included outcome reported (e.g., definition of outcome measure; timing of measurement; scale of measurement; and effect size as presented, including mean difference, risk ratio, odds ratio, or hazard ratio, or arm-level data necessary to calculate an effect size). Measures of variability and statistical tests used were also be extracted (standard deviation, 95% CI, standard error, p-values).

8.8 *Data preparation*

Many of the included studies did not present adequate data for key findings to enable inclusion *prima facie* in a meta-analysis model. We used a variety of published methods to derive the necessary data.

Across all studies, we used data for the point of greatest maturity (i.e., last available follow-up) for which effect sizes were estimable. In studies presenting estimates with confirmed relapses and with non-confirmed relapses, we selected estimates with confirmed relapses.

We used rate ratios (abbreviated as RR in the text) to examine relapse outcomes (e.g. the ratio of annualised relapse rates in two study arms). We used summary statistics instead of attempting to approximate individual participant data for each arm, in part due to the use of stratification in estimating study findings. Where necessary, we imputed standard errors by estimating the number of events in each arm (e.g. when relapse rates were analysed using an analysis of variance, or ANOVA, model with Gaussian link, instead of the preferred Poisson distribution for count variables). When arm-level annualised relapse rates (ARRs) were presented without Poisson-based standard errors, we generally assumed that the ARR presented for study arms was a fair approximation and then re-estimated the standard errors for the rate ratio using all available information on person-years of follow-up and number of relapses. Rate ratios were then analysed using a lognormal distribution.

We used hazard ratios (abbreviated as HR in the text) to examine time to event outcomes (e.g. time to first relapse or time to confirmed disability progression). Where hazard ratios were not estimated from a Cox proportional hazards model, we used several methods in order of priority. First, we used methods published by

Tierney et al. (2007)[163] to estimate the HR, in particular using the number of patients analysed, the number of total events and the p-value derived from a log-rank test. When those data were not available to us, we then used the final predicted probabilities of survival in each study arm (generally estimated using Kaplan-Meier curves) and estimated the cumulative hazard using the equation $-\ln(S(t))$, where $S(t)$ is the probability of survival at time t. We then took the ratio of the cumulative hazards and used the log-rank p-value to approximate the standard errors for the HR, under the property that the p-value from the log-rank test for survival asymptotically approaches the p-value from a likelihood ratio test derived from a Cox proportional hazards model.

We used dichotomous outcomes to examine discontinuation due to adverse events.

8.9 *Narrative synthesis and meta-analysis*

Narrative synthesis of studies and meta-analyses were organised hierarchically: first by MS subtype, then by intervention-comparator contrast, and finally by each outcome for which data were available. Within each MS subtype, we examined included studies for similarity. When studies were sufficiently similar, we estimated both pairwise and network meta-analyses. First, we pooled outcomes for each intervention-comparator contrast and by MS subtype using random effects meta-analysis in Stata v14 and examined these pairwise meta-analyses for heterogeneity, measured as Cochran's Q and I^2.

Subsequently, we used the package -network-[164] in Stata v14 to estimate network meta-analyses. Because -network- operates in a frequentist paradigm, there was no need to sensitivity analyse on prior distributions. Where possible, we estimated meta-analyses using random effects; however, some sparse networks, where there were few studies for each contrast between two treatments, required the use of a fixed effects model. We used a common heterogeneity model, where the between-studies variance is assumed equal across comparisons.

After estimating a consistency model (i.e. where direct evidence for a contrast between two treatments is assumed to agree with indirect evidence for that contrast), we checked networks that were not star-shaped in design for inconsistency using two methods. We estimated a design-by-treatment interaction model and examined both the design effects and the overall Wald test for evidence for inconsistency. We also used the side-splitting method to test for differences in the effectiveness estimates between direct and indirect evidence. Where evidence of inconsistency existed, we considered the direction of that inconsistency.

Finally, we used a bootstrapping method to resample from our estimates of intervention effectiveness and develop probabilities of each treatment's relative position to the others. We then used the surface under the cumulative ranking curve (SUCRA) to produce a unified ranking of treatments.

8.9.1 Meta-analyses for CIS

We estimated a network meta-analysis for time to clinically definite MS in patients with CIS. This was the outcome most consistently reported across studies and matched most closely with the decision problem in the NICE scope.

8.9.2 Meta-analyses for RRMS and SPMS

Relapse outcomes and relapse severity

We elected to meta-analyse rate ratio of relapses as an overall measure of relapses in RRMS and SPMS. Though we narratively synthesised analyses for time to relapse and proportion free of relapses, both measures had significant issues; in particular, time to relapse data were inconsistently presented and at times impossible to impute, and proportion relapse-free would have been especially dependent on duration of follow-up and would not have captured the impact of drugs on multiple relapses per person.

We elected to meta-analyse two measures for relapse severity in RRMS: steroid-treated relapses and relapses described as moderate or severe. These were the most commonly reported measures.

Disability progression

We elected to meta-analyse time to disability progression as a measure of disability progression in RRMS and SPMS. We separated estimates for disability progression confirmed at 3 months and confirmed 6 months, as we could not establish whether measures were commensurate. Though we narratively synthesised proportions of patients with disability progression and magnitude of EDSS change, we elected not to meta-analyse these as proportions and magnitude of EDSS change would have been especially dependent on duration of follow-up; in particular, data for magnitude of EDSS change would have required extensive imputation.

Discontinuation due to adverse events

We estimated models for discontinuation due to adverse events (AEs). In order to estimate these models, we examined three outcomes as reported: discontinuation of study drug due to AEs, discontinuation of study due to AEs, and withdrawal from study due to AEs. In the few studies that reported both discontinuation of study drug due to AEs and discontinuation of study due to AEs, we chose discontinuation of study drug due to AEs as we believed it would be a closer match to capturing the relationship between study drugs and discontinuation. We also estimated one model with studies closest to 24 months of follow-up as risk of discontinuation due to AEs is not an annualised measure, like ARR, or an 'instantaneous' measure, like HR, and we could not reliably estimate person-years of follow-up in each arm across all studies to convert study-level estimates to rate ratios.

8.10 *Publication bias*

Were we to have had more than 10 studies for an intervention-comparator contrast, we would have used funnel plots to examine studies for the presence of publication bias in pairwise comparisons.

8.11 *Industry submissions regarding effectiveness of treatments*

We examined company submissions and present summaries and appraisal of their clinical effectiveness analyses in Section 10 below.

9 RESULTS OF ASSESSMENT OF CLINICAL EFFECTIVENESS

9.1 *Search results*

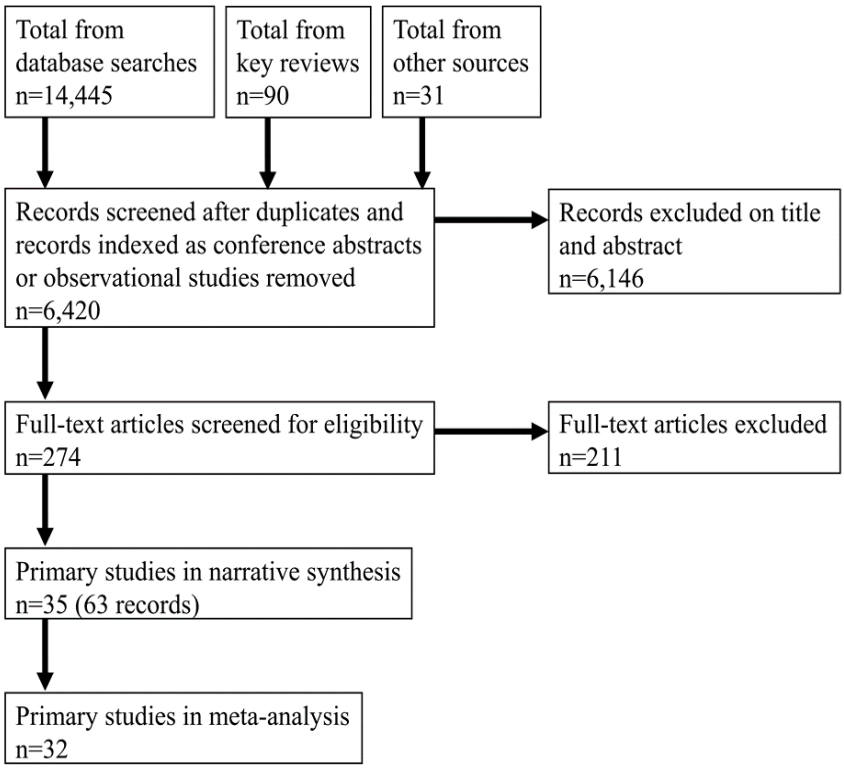
9.1.1 Included studies

The search identified 6,420 potentially relevant records. We removed 6,146 records that did not meet our inclusion criteria at title/abstract stage, leaving 274 records to be examined at full-text. Among these, we excluded 211 leading to 63 publications meeting our inclusion criteria and corresponding to 35 primary studies. Of these primary studies, 32 were included in at least one meta-analysis. The flow diagram describing the process of identifying relevant literature can be found in Figure 1.

9.1.2 Excluded studies

The reasons for exclusion are presented both across records excluded at full text and for each record individually in Appendix 3.

Figure 1: PRISMA flowchart, clinical effectiveness reviews



9.2 *Systematic reviews used to locate primary studies*

Three Cochrane reviews were identified as being of particular relevance to this study, and contributed to the identification of original studies for inclusion. These reviews were Tramacere 2015,[155] Filippini *et al.* 2013[156] and Clerico *et al.* 2008.[154]

9.2.1 Scope and aims

Overview

Filippini et al. aimed to review clinical effectiveness of immunosuppressors and immunomodulators in all MS types [156] and to rank them based on relapse rate, disability progression and acceptability. Tramacere *et al.* aimed to review and rank these agents in RRMS specifically [155]. Clerico and colleagues examined IFN β-1a, IFN β-1b and GA for delaying the conversion of CIS into MS [154], though this analysis was undertaken before revised diagnostic criteria classed many CIS episodes as in fact being RRMS.[62]

Diagnostic criteria used to identify studies

Tramacere et al.[155] used all four sets of diagnostic criteria [62, 64, 66, 165] to identify RCTs of treatment for RRMS with participants over 18 years old.

Filipinni and colleagues[156] included RCTs only, investigating treatment of adults over 18 with MS diagnosed according to Poser,[64] the original McDonald criteria,[165] or the 2005 modified McDonald criteria.[66] Therefore this review included all types of MS. However, it did not incorporate the most recent revision of the McDonald criteria[62], and so excluded CIS studies.

In contrast, Clerico and colleagues[154] used the Poser criteria to identify RCTs and pseudorandomised double-blinded trials of CIS, with reference to specific MRI findings. No exclusion criteria based on study participant age were specified.[166]

Included interventions

Tramacere and colleagues[155] included all immunomodulators and immunosuppressors, even if unlicensed. These included the IFN and GA drugs specified in NICE's scope, as well as 11 other interventions. We noted that the review by Tramacere et al. excluded the Calabrese 2012 study stating that it was non-randomised. To the best of our knowledge, this study is a RCT and it has been included in our review.

The interventions studied by Filippini *et al.* included IFN and GA formulations licenced at the time (i.e. not pegylayed IFN), as well as seven other interventions.[156] Clerico *et al.* would have included licenced IFN and GA interventions (i.e. not pegylated IFN), but only identified three studies comparing IFN to placebo.[155]

All three reviews included studies evaluating DMTs with a dose regimen currently not recommended or authorised (for example, IFN β-1a (Rebif) given once weekly instead of three times weekly). The Cochrane reviews did not account separately for the inclusion of studies with a DMT given under a non-recommended dose regimen in a sensitivity analysis.

9.2.2 Outcomes

Tramacere et al.[155] and Filippini et al.[156] examined risk of relapse over 12 months and 24 months as a dichotomous outcome, as well as presence or absence of disability progression assessed using EDSS. In Filippini et al.,[156] which included progressive forms of multiple sclerosis as well as RRMS, risk of disability progression was reported as the first outcome.

Both reviews assessed adverse events. Filippini et al.[156] also included incidence of relapse over 36 months, and assessments of acceptability of treatment as measured by discontinuation due to adverse events.

Clerico et al.[154] used proportion converting to clinically definite MS as the primary outcome, alongside annualised relapse rate and additional MRI outcomes.

9.2.3 Statistical methods

In Tramacere et al.,[155] network meta-analyses were performed for primary outcomes. Random effects models were used within a frequentist setting. In contrast, Filippini et al.[156] performed network meta-analyses within a Bayesian framework. For both reviews, equal heterogeneity across comparisons was assumed, and any correlations induced by multi-arm studies were accounted for. Both used Surface Under the Cumulative Ranking curve (SUCRA) to describe the ranking of treatments.[167]

9.2.4 Review findings

Tramacere et al.[155] found that in RRMS, the SUCRA for the chance of experiencing relapse over 12 months for GA was 52%, for subcutaneous IFN β-1a (Rebif) 36%, for pegylated IFN β-1a 33%, for IFN β-1b 27% and for intramuscular IFN β-1a (Avonex) it was 25%. The risk ratio of GA vs. placebo for this outcome was 0.80 (95% CI [0.68, 0.93]) whereas all other interventions of interest did not return significant results. The ranking of interventions of interest for prevention of relapse over 24 months in RRMS was GA (most successful), followed by IFN β-1b, subcutaneous IFN β-1a (Rebif), and intramuscular IFN β-1a (Avonex).

SUCRA plots for reducing the worsening of disability over 24 months in RRMS returned results of 58% for GA, 51% for IFN β-1b, 36% for subcutaneous IFN β-1a (Rebif), and 21% for intramuscular IFN β-1a (Avonex). The only interventions of interest with sigificant risk ratios as compared to placebo were GA (0.77, 95% CI [0.64, 0.92]), and IFN β-1b (0.79, [0.65, 0.97]).

Thus, in the Tramacere et al[155] review, GA performed the best of the interventions of interest. Intramuscular IFNb1a (Avonex) was consistently the least effective intervention. However, other interventions included in the Cochrane review (but which are outwith the scope of the current MTA) performed better, such as alemtuzumab (SUCRA: 97%, risk ratio vs. placebo 0.40, 95% CI [0.31, 0.51]).

Filippini et al.[156] returned similar rankings derived from SUCRA values for reducing recurrence of relapses over 12 months. However, for reducing recurrence of relapses at 24 months, the SUCRA values resulted in different rankings: subcutaneous IFNb1a (Rebif), GA, IFN β-1b, and for intramuscular IFN β-1a (Avonex). In terms of reducing disability progression over 24 months, GA ranked best (SUCRA 67%), followed by IFN β-1b (54%),

subcutaneous IFN β-1a (Rebif) (47%), and intramuscular IFN β-1a (Avonex) (18%).

In Clerico et al.,[155] only direct treatment comparisons were performed, using conventional pairwise meta-analyses to compare IFN to placebo. No studies of GA were identified, but IFN was effective against placebo.

9.2.5 Review quality

All three Cochrane Reviews scored 10/11 on the AMSTAR checklist, and were assessed as being of high methodological quality. Tramacere et al.[155] and Filippini et al.[156] inadequately reported grey literature searching, and Clerico et al.[154] did not assess the risk of publication bias.

9.3 *Study characteristics and methodological quality*

9.3.1 Study and participant characteristics

We included 35 primary studies published between 1987 and 2015, which involved 14,623 participants randomly assigned to IFN-β, GA, or placebo added to standard care, or best supportive care alone. The median follow-up was 24 months. Only 4 studies were conducted at single centres. The median number of participating centers was 30.5 (range, 1 to 200). The majority of studies were international (57.1%). Twenty-two (63%) were placebo-controlled, 12 (34%) were head-to-head studies with a comparison between one IFN and GA or between two IFNs, and two (6%) compared an IFN to no treatment (standard care). Of the 22 placebo-controlled studies, 3 aimed to evaluate the effectiveness of DMTs that were excluded in the scope (laquinimod, daclizumab, and dimethyl-fumarate) compared to placebo, with IFN-beta or glatiramer being added as a third descriptive arm. Given the different posology and method of administration between these agents used in the 3 studies (two were oral drugs, one was an IV drug), the comparison of IFN-β or GA to placebo was not blinded.

The key characteristics of included studies are provided in Table 4. A full list of publications is in Appendix 4.

Table 4. Characteristics of included studies.

Study ID MS type (diagnostic criteria) Included in TA32?	Study details	Characteristics of participants at baseline	Intervention	Participants
ADVANCE 2014 RRMS (2005 McDonald criteria)	**Country:** USA, Belgium, Bulgaria, Canada, Chile, Colombia, Croatia, Czech Republic, Estonia, France, Georgia, Germany, Greece, India, Latvia, Mexico, Netherlands, New Zealand, Peru, Poland, Romania, Russian Federation, Serbia, Spain, Ukraine, United Kingdom. **No. of countries:** 26 **Centres**: 183 **Study period**: June 2009 and November 2011. **Sponsor**: Biogen Idec	**Mean age**: 36.5 (9.9) **Mean sex**: 71% female **Race**: 82% white **EDSS Score**: 2.5 **Relapse rate**: 1.6 within the previous 12 months, 2.6 within the previous 36 months **Time from diagnosis of MS**: 3.6 years **Other clinical features of MS**: Time from first MS symptoms: 6.6 years	**Arm 1**: pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy) **Arm 2**: Placebo	**Randomised** 512 arm 1 500 arm 2
AVANTAGE 2014 RRMS/CIS, diagnostic criteria unclear	**Country**: France **No. of countries:** 1 **Centres**: 61 **Study period**: March 2006-April 2008, 3 months follow up **Sponsor**: Bayer	**Mean age**: 38.7 **Mean sex**: 75% female **Race**: NA **EDSS Score**: *1.8 ± 1.3* **Mean number of relapse rate**: 2.1 ± 1.1 **Time from diagnosis of MS**: 3.3 (6.4) years **Other clinical features of MS**: NA	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) via Betaject **Arm 2**: IFN β-1b 250 µg SC every other day (Betaferon) via Betaject light **Arm 3**: IFN β-1a 44 SC three times weekly (Rebif) via Rebiject II	**Included:** 73 arm 1 79 arm 2 68 arm 3
BECOME 2009 RRMS/CIS (likely McDonald 2001 or 2005)	**Country:** USA **No. of countries:** 1 **Centres**: 2 **Study period**: Not specified, follow up over 2 years **Sponsor**: Bayer Schering pharma	**Mean age**: 36 **Mean sex**: 69% females **Race**: 52% white **Median EDSS Score**: *2* **Relapse rate**: 1.8 and 1.9 ARR **Time from diagnosis of MS**: between 0.9 and 1.2 **Other clinical features of MS**: 81% RRMS, 19% CIS; MSFC median 0.13	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) **Arm 2**: GA 20 mg SC daily (Copaxone)	**Randomised** 36 arm 1 39 arm 2
BENEFIT 2006 CIS (Poser, McDonald 2001)	**Country:** Israel, Canada, and 18 European countries including Germany, Spain, United Kingdom, France, Netherlands, Switzerland **No. of countries:** 20 **Centres**: 98	**Median age:** 30 **Mean sex**: 70.7% female **Race**: 98.3% white **EDSS Score (median)**: 1.5	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon)	**Randomised** 305 arm 1 182 arm 2

Study ID MS type (diagnostic criteria) Included in TA32?	Study details	Characteristics of participants at baseline	Intervention	Participants
	Study period: February 2002 and June 2003. 24 month follow up **Sponsor**: Schering AG	**Relapse rate**: NA **Time from diagnosis of MS**: Not specified **Other clinical features of MS**: monofocal / plurifocal onset : 52.6%/47.4%	**Arm 2**: Injections of placebo	
BEYOND 2009 RRMS (McDonald 2005)	**Country:** Not specified **No. of countries:** 26 **Centres**: 198 **Study period**: November, 2003, and June, 2005. Follow up between 2-3.5 years **Sponsor**: Bayer	**Mean age** 35.6 **Mean sex**: 69.4% female **Race**: 91.9% white **EDSS Score**: 2.33 **Relapse rate**: 1.6 relapses in last year **Time from diagnosis of MS**: 5.2 years **Other clinical features of MS**: 3.6 relapses previously; 70.6% had two or more relapses in past 2 years	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) **Arm 2:** GA 20 mg SC daily (Copaxone)	**Randomised** 897 arm 1 448 arm 2
Bornstein 1987 RRMS (Poser) Included in TA32	**Country:** USA **No. of countries**: 1 **Centres**: Not specified **Study period**: Not specified, follow up over 2 years **Sponsor**: public (grant from the National Institute of Neurological and Communicative Disorders and Stroke and grant from the National Institutes of Health)	**Mean age**: 30.5 **Mean sex**: 42% male/58% female **Race**: 96% white **EDSS Score**: *3.11* **Relapse rate**: 3.85 over 2 years **Time from diagnosis of MS**: 5.5 years duration of disease **Other clinical features of MS**: NA	**Arm 1**: GA 20 mg SC daily (Copaxone) **Arm 2**: Placebo	**Randomised** 25 arm 1 25 arm 2
BRAVO 2014 RRMS (McDonald 2005)	**Country:** US, Bulgaria, Croatia, Czech Republic, Estonia, Georgia, Germany, Israel, Italy, Lithuania, Macedonia, Poland, Romania, Russia, Slovakia, South Africa, Spain, Ukraine and others not specified **No. of countries:** 18 **Centres**: 140 **Study period**: April 2008 to June 2011. 24 months follow up **Sponsor**: Teva Pharmaceutical Industries	**Mean age:** Median: 37.5 placebo, 38.5 IFN **Mean sex**: 71.3% females in placebo arm, 68.7% females in IFN arm **Race**: N/A **EDSS Score**: Median: 2.5 placebo, 2.5 IFN **Median Relapse rate**: previous year: 1.0 placebo, 1.0 IFN; previous 2 years: 2.0 placebo, 2.0 IFN **Median Time from diagnosis of MS**: 1.2 placebo, 1.4 IFN **Other clinical features of MS**: NA	**Arm 1**: IFN β-1a 30 µg IM once weekly (Avonex) **Arm 2**: Oral placebo once-daily with neurologist monitoring	**Randomised** 447 arm 1 450 arm 2

Study ID MS type (diagnostic criteria) Included in TA32?	Study details	Characteristics of participants at baseline	Intervention	Participants
Calabrese 2012 RRMS (McDonald 2005)	**Country:** Italy **No. of countries:** 1 **Centres**: 1 **Study period**: 1 Jan 2007 – 30 June 2008 Follow up over 2 years **Sponsor**: grant from Merck Serono S.A	**Mean age**: 36.5 (9.9) **Mean sex**: 70.2% of female/20.8 % of male **Race**: NA **EDSS Score**: 2.1 (1.1) **Relapse rate**: 1.2 (0.7) **Time from diagnosis of MS**: 5.6 years (2.4) **Other clinical features of MS**: None	**Arm 1**: IFN β-1a 44 SC three times weekly (Rebif) **Arm 2**: IFN β-1a 30 µg IM once weekly (Avonex) **Arm 3**: GA 20 mg SC daily (Copaxone)	**Randomised** 55 arm 1 55 arm 2 55 arm 3
CHAMPS 2000 CIS (Poser)	**Country:** USA and Canada **No. of countries:** 2 **Centres**: 50 **Study period**: April 1996 until March 2000. Follow up 36 months **Sponsor**: Biogen	**Mean age** 33.0 (0.7) **Mean sex**: 75% female **Race**: 86% white **EDSS Score**: *NA* **Relapse rate**: NA **Time from diagnosis of MS**: NA **Other clinical features of MS**: Type of initial event: optic neuritis (50%), Spinal cord syndrome (22%), Brainstem or cerebellar syndrome (28%) Type of onset (based on new classification): monofocal, 70%; multifocal, 30% Duration of symptoms before initiation of intravenous methylprednisolone: 8 days Duration of symptoms at initiation of study treatment: 19 days	**Arm 1**: IFN β-1a 30 µg IM once weekly (Avonex) **Arm 2**: Placebo	**Randomised** 193 arm 1 190 arm 2
CombiRx 2013 RRMS (McDonald 2001, Poser)	**Country:** United States, Canada **No. of countries:** 2 **Centres**: 68 **Study period**: January 2005-April 2012. Minimally 36 months follow up **Sponsor**: NIH, with materials provided by Biogen and Teva	**Mean age** 38.3 **Mean sex**: 70.3% female **Race**: 87.6% white **EDSS Score**: 2.0 **Relapse rate**: 1.7 relapses in last year, on average **Time from diagnosis of MS**: 1.2 **Other clinical features of MS**:	**Arm 1**: IFN β-1a 30 µg IM once weekly (Avonex) **Arm 2**: GA 20 mg SC daily (Copaxone)	**Randomised** 250 arm 1 259 arm 2

Study ID MS type (diagnostic criteria) Included in TA32?	Study details	Characteristics of participants at baseline	Intervention	Participants
		NA		
CONFIRM 2012 RRMS (McDonald 2005)	**Country:** USA, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Canada, Costa Rica, Croatia, Czech Republic, Estonia, France, Germany, Greece, India, Ireland, Israel, Latvia, Macedonia, Mexico, Republic of Moldova, New Zealand, Poland, Puerto Rico, Romania, Serbia, Slovakia, Spain, Ukraine **No. of countries:** 28 **Centres**: 200 **Study period**: 2 year follow up **Sponsor**: Biogen idec	**Mean age** 36.8 **Mean sex**: 70% female **Race**: 84% white **EDSS Score**: 2.6 **Relapse rate**: 1.4 in prior 12 months **Time from diagnosis of MS**: 4.6 years **Other clinical features of MS**: any prior DMTs (%)=29%	**Arm 1**: GA 20 mg SC daily (Copaxone) **Arm 2**: 2 placebo capsules orally thrice daily	**Randomised** 360 arm 1 363 arm 2
Cop1 MSSG 1995 RRMS (Poser) Included in TA32	**Country:** USA **No. of countries:** 1 **Centres**: 11 **Study period**: October, 1991, and May, 1992. 2 year follow up. **Sponsor**: the FDA orphan drug program, the National multiple sclerosis society, and TEVA pharmaceutical	**Mean age** 34.4. **Mean sex**: 73% female **Race**: 94% white **EDSS Score**: 2.6 **Relapse rate**: 2.9 prior 2-year rate **MS duration**:6.9 years **Other clinical features of MS**: ambulation index= 1.1	**Arm 1**: GA 20 mg SC daily (Copaxone) **Arm 2**: Placebo	**Randomised** 125 arm 1 126 arm 2
ECGASG 2001 RRMS (Poser) Included in TA32 (unpublished at the time)	**Country:** Canada **No. of countries:** 7 **Centres**: 29 **Study period**: Enrollment started in February 1997 and concluded in November 1997. 9 month follow up **Sponsor**: Teva Pharmaceutical Industries	**Mean age** 34 **Mean sex**: NA **Race**: NA **EDSS Score**: 2.4 **Relapse rate**: 2.65 **Disease duration (years):** 8.1 **Other clinical features of MS**: ambulation index=1.15	**Arm 1**: GA 20 mg SC daily (Copaxone) **Arm 2**: Placebo SC injections	**Randomised** 119 arm 1 120 arm 2
ESG 1998 SPMS (Poser, Lublin 1996) Included in TA32	**Country:** European countries **No. of countries:** NA **Centres**: 32 **Study period**: 36 month follow up **Sponsor**: Schering AG	**Mean age** 41.0 **Mean sex**: 61% female **Race**: NA **EDSS Score**: 5.15 **Relapse rate**: NA **Time from diagnosis of MS**: NA **Other clinical features of MS**: Patients without relapses in 2 years before inclusion: 30% Mean disease duration: 13.1 years	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) **Arm 2**: SC injections of placebo	**Randomised** 360 arm 1 358 arm 2

Study ID MS type (diagnostic criteria) Included in TA32?	Study details	Characteristics of participants at baseline	Intervention	Participants
		Time from diagnosis of relapsing risk MS (years): 8.15 Mean time since evidence of deterioration (years): 3.8 Mean time since diagnosis of SP-MS (years): 2.15		
Etemadifar 2006 RRMS (Poser)	**Country:** Iran **No. of countries:** 1 **Centres**: 1 **Study period**: September 2002 and September 2004. 24 month follow up **Sponsor**: Not specified	**Mean age** 28.5 **Mean sex**: 76% female **Race**: NA **EDSS Score**: 2.0 **Relapse rate 1 year prior** : 2.2 **Time from diagnosis of MS**: 3.2 years **Other clinical features of MS**: None	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) **Arm 2**: IFN β-1a 30 µg IM once weekly (Avonex) **Arm 3**: IFN β-1a 44 SC three times weekly (Rebif)	**Randomised** 30 arm 1 30 arm 2 30 arm 3
EVIDENCE 2007 RRMS (Poser)	**Country:** USA, France, UK, Norway, Austria, Germany, France, Finland, Sweden, Canada **No. of countries:** 10 **Centres**: 56 **Study period**: Unclear. Minimally 48 weeks follow up, average 64.2 **Sponsor**: Serono	**Mean age** 37.9 **Mean sex**: 74.8% female **Race**: 91.0% Caucasian **EDSS Score**: 2.3 Median: 2.0 **Relapse rate**: 2.6 Median 2.0 relapses in last 2 years **Duration of MS**: 6.6. Median: 4.0-4.1 years **Other clinical features of MS**: Time since last relapse (months): Median 3.9 to 4.4; mean 5.1	**Arm 1**: IFN β-1a 44 SC three times weekly (Rebif) **Arm 2**: IFN β-1a 30 µg IM once weekly (Avonex)	**Randomised** 339 arm 1 338 arm 2
GALA 2013 RRMS (McDonald 2005)	**Country:** United States, Bulgaria, Croatia, Germany, Poland, Romania, and Ukraine and others **No. of countries:** 17 **Centres**: 142 **Study period**: Not specified. 12 months follow up. **Sponsor**: TEVA pharmaceutical industries	**Mean age** 37.6 **Mean sex**: 68% female **Race**: 98% Caucasian **EDSS Score**: 2.7 **Relapse rate**: 1.3 in the prior 12 months, 1.9 in the prior 24 months **Time from diagnosis of MS**: NA **Other clinical features of MS**: Time from onset of first symptoms of MS=7.7 years	**Arm 1**: GA 40 mg SC three times weekly (Copaxone) **Arm 2**: SC placebo injections	**Randomised** 943 arm 1 461 arm 2

Study ID MS type (diagnostic criteria) Included in TA32?	Study details	Characteristics of participants at baseline	Intervention	Participants
GATE 2015 RRMS (McDonald 2010)	**Country:** USA, Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Georgia, Germany, Italy, Mexico, Republic of Moldova, Poland, Romania, Russian Federation, Serbia, South Africa, Ukraine, United Kingdom **No. of countries:** 20 **Centres**: 118 **Study period**: Recruited between December 7, 2011, and March 21, 2013; last follow-up December 2, 2013. Follow up 9 months (double-blind follow-up) + additional 15 months (open-label) **Sponsor**: Synthon BV	**Mean age** 33.1 **Mean sex**: 66.4% female **Race**: NA **EDSS Score**: 2.7 **Relapse rate**: 1.9 in prior 2 years **Time from diagnosis of MS**: NA **Other clinical features of MS**: • Time to onset of first symptoms to randomisation (years): 5.9 • No history of prior disease treatment: 16.1%	**Arm 1**: GA 20 mg SC daily (Copaxone) **Arm 2**: Placebo	**Randomised** 357 arm 1 84 arm 2
IFNB MSSG 1995 RRMS (Poser) Included in TA32	**Country:** USA and Canada **No. of countries:** 2 **Centres**: 11 **Study period**: after 2 years of follow-up, all subjects were given the option of continuing treatment in a double-blind fashion, extending the total treatment period to 5.5 years for some patients **Sponsor**: Triton Biosciences, Berlex Laboratories	**Mean age** 35.6 **Mean sex**: 70% female **Race**: 94% white **EDSS Score**: 2.9 **Relapse rate**: 3.5 in prior 2 years **Time from diagnosis of MS**:4.3 years **Other clinical features of MS**: Baseline Scripps neurological rating scale: 80.8	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) **Arm 2**: SC injections placebo	**Randomised** 124 arm 1 123 arm 2
IMPROVE 2012 RRMS (McDonald 2005)	**Country:** Italy, Germany, Serbia, Canada, Bulgaria, Estonia, Lithuania, Romania, Russia, Spain **No. of countries:** 10 **Centres**: 5 **Study period**: December 2006 to February 2009. Follow up 16 weeks for the double-blind phase, then 24 weeks where all patients received interferon beta 1-a, at last 4 weeks of safety period observation **Sponsor**: Merck Serono S.A.	**Mean age** NA **Mean sex**: NA **Race**: NA **EDSS Score**: NA **Relapse rate**: NA **Time from diagnosis of MS**: NA **Other clinical features of MS**: NA	**Arm 1**: IFN β-1a 44 SC three times weekly (Rebif) **Arm 2**: SC injections of placebo	**Randomised** 120 arm 1 60 arm 2
INCOMIN 2002 RRMS (Poser)	**Country:** Italy **No. of countries:** 1 **Centres**: 15 **Study period**: October, 1997, and June, 1999. 2 year follow up **Sponsor**: Istituto Superiore di Sanita' of the Italian Ministry of Health and the Italian MS Society	**Mean age** 36.9 **Mean sex**: 65% female **Race**: NA **EDSS Score**: 1.97 **Relapse rate 2 years prior**: 1.45 **Time from diagnosis of MS**: 6.3 years	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) **Arm 2**: IFN β-1a 30 µg IM once weekly (Avonex)	**Randomised** 92 arm 1 96 arm 2

Study ID MS type (diagnostic criteria) Included in TA32?	Study details	Characteristics of participants at baseline	Intervention	Participants
		Other clinical features of MS: None		
Kappos 2011 RRMS (McDonald 2001)	**Country:** Belgium, Bulgaria, Canada, Czech Republic, Denmark, France, Germany, Italy, Mexico, Romania, Russian Federation, Serbia, Slovakia, Spain, Switzerland, Ukraine, United Kingdom, USA and others **No. of countries:** 20 **Centres**: 79 **Study period**: Not specified. Up to 96 weeks follow up. **Sponsor**: F Hoffmann-La Roche Ltd, Biogen Idec Inc	**Mean age** 37.5 **Mean sex**: 65% female **Race**: 96% white **EDSS Score**: 3.3 **Relapse rate**: NA **Time from diagnosis of MS**: median only **Other clinical features of MS**: NA	**Arm 1**: IFN β-1a 30 µg IM once weekly (Avonex) **Arm 2**: placebo injection every other week	**Randomised** 55 arm 1 54 arm 2
Knobler 1993 RRMS (Poser)	**Country:** USA **No. of countries:** 1 **Centres**: 3 **Study period**: June and October 1986. Follow up 3 years (24 weeks of initial follow-up for the 5 groups then all the patients that had received 0.8mU, 4MU and 16MU for 24 weeks received a dose of 8MU from week 24 to 3 years) **Sponsor**: Triton Biosciences, Inc and Berlex Laboratories, Inc	**Mean age** 35.6 **Mean sex**: 48% female **Race**: NA **EDSS Score**: 3.1 **Mean exacerbation in prior 2 years**: 2.84 **Time from diagnosis of MS**: 6.6 years **Other clinical features of MS**: mean Scripps Neurological Rating Scale (NRS): 76.6	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) **Arm 2**: Subcutaneous injection of placebo (1mL like Betaseron 8 MU)	**Randomised** 6 arm 1 7 arm 2
MSCRG 1996 RRMS (Poser) Included in TA32	**Country:** USA **No. of countries:** 1 **Centres**: 4 **Study period**: November, 1990 to early 1993 2 years follow up for all-patients + 2 additional years for patients completing dosing before the end of the first period of follow-up. **Sponsor**: National Institutes of Health, National Institute of Neurological Disorders and Stroke (NINDS) grant R01-26321 and Biogen, Inc.	**Mean age** 36.8 **Mean sex**: 73.7% female **Race**: 93% white **EDSS Score**: *2.4* **Relapse rate**: 1.2 **MS duration (years):** 6.5 **Other clinical features of MS**: None	**Arm 1**: IFN β-1a 30 µg IM once weekly (Avonex) **Arm 2**: Placebo	**Randomised** 158 arm 1 143 arm 2
NASG 2004 SPMS (Poser, Lublin 1996)	**Country:** US/Canada **No. of countries:** 2 **Centres**: 35 **Study period**: Unclear. 3 year follow up **Sponsor**: Biogen	**Mean age** 46.8 **Mean sex**: 63.2% female **Race**: NA **EDSS Score**: 5.1 **Relapse rate**: Relapses in two years prior to study: 0.8 **Time from diagnosis of MS**: 14.7 years **Other clinical features of MS**:	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) **Arm 2**: Injectable placebo (note two types, one calibrated to body surface area)	**Randomised** 317 arm 1 308 arm 2

Study ID MS type (diagnostic criteria) Included in TA32?	Study details	Characteristics of participants at baseline	Intervention	Participants
		Time from SPMS diagnosis: 4.0 years Those relapse-free in two years prior to study: 55%		
Pakdaman 2007 CIS (Poser)	**Country:** Iran **No. of countries:** 1 **Centres**: 4 **Study period**: February 2002 to August 2005. 36 months follow up **Sponsor**:Unclear	**Mean age** 28.0 **Mean sex**: 67.8% female **Race**: NA **EDSS Score**: NA **Relapse rate**: NA **Time from diagnosis of MS**: NA **Other clinical features of MS**: Type of initial event: optic neuritis 48.0%, spinal cord syndrome 23.8%, brain/cerebellar syndrome 21.8%	**Arm 1**: IFN β-1a 30 µg IM once weekly (Avonex) **Arm 2**: Injectable placebo	**Randomised** 104 arm 1 98 arm 2
PreCISe 2009 CIS (McDonald 2005, Poser)	**Country:** Italy, Romania, Argentina, Finland, Austria, Germany, Sweden, Australia, Hungary, France, Norway, Spain, Denmark, Canada, USA, United Kingdom, **No. of countries:** 16 **Centres**: 80 **Study period**: Enrolled from January, 2004, to January, 2006. 36 months follow up **Sponsor**: Teva Pharmaceutical Industries	**Mean age** 31.2 (6.9) **Mean sex**: 67% FEMALE **Race**: 96% white **EDSS Score**: 1.0 (1.0) **Relapse rate**: NA **Time from diagnosis of MS**:NA **Other clinical features of MS**: Time from first symptom (days): mean=74.0 (14.1); median=78.8 (33–104)	**Arm 1**: GA 20 mg SC daily (Copaxone) **Arm 2**: Daily placebo injections	**Randomised** 243 arm 1 238 arm 2
PRISMS 1998 RRMS (Poser) Included in TA32	**Country:** Australia, Belgium, Canada, Finland, Germany, Netherlands, Sweden, Switzerland, UK **No. of countries:** 9 **Centres**: 22 **Study period**: May 1994 to February 1995 with 2 years follow up. **Sponsor**: Ares- Serono	**Mean age** Median: 34.9 **Mean sex**: 69% female **Race**: NA **EDSS Score**: 2.5 (SD 1.2) **Relapse rate**: 3.0 (SD 1.2) **Time from diagnosis of MS**: Median: 5.3 years) **Other clinical features of MS**: NA	**Arm 1**: IFN β-1a 22 µg SC three times weekly (Rebif) **Arm 2**: IFN β-1a 44 SC three times weekly (Rebif) **Arm 3**: Placebo	**Randomised** 189 arm 1 184 arm 2 187 arm 3
REFLEX 2012 CIS (McDonald 2005)	**Country:** Argentina, Austria, Belgium, Bulgaria, Canada, Croatia, Czech Republic, Estonia, Finland, France, Germany, Greece, Israel, Italy, Latvia, Lebanon, Morocco, Poland, Portugal, Romania, Russian Federation, Saudi Arabia, Serbia, Slovakia, Spain, Turkey **No. of countries:** 26	**Mean age** 30.7 **Mean sex**: 66% female **Race**: NA **EDSS Score**: median 1.5 **Relapse rate**: NA	**Arm 1**: IFN β-1a 44 SC three times weekly (Rebif) **Arm 2**: Thrice weekly injections	**Randomised** 146 arm 1 146 arm 2

Study ID MS type (diagnostic criteria) Included in TA32?	Study details	Characteristics of participants at baseline	Intervention	Participants
	Centres: 80 **Study period**: November, 2006 to August, 2010. 24 month double-blind follow up, plus 12 months for optional open label extension **Sponsor**: Merck Serono SA	**Time from diagnosis of MS**:NA **Other clinical features of MS**: Time since first demyelinating event (days)= 57.6) Fulfilling McDonald 2010 MS criteria: 37.7% (from Freedman 2014)		
REFORMS 2012 RRMS (McDonald 2005, Poser)	**Country:** USA **No. of countries:** 1 **Centres**: 27 **Study period**: December 2006-November 2007. 12 weeks follow up **Sponsor**: EMD Serono, Pfizer	**Mean age** 40.52 (SD 9.65) **Mean sex**: 70% female **Race**: 87.6% white **EDSS Score**: NA **Relapse rate**: 1.33 (SD 0.49) (of those with relapses) **Time from diagnosis of MS**: 1.47 yrs (3.31) **Other clinical features of MS**: Percentage with no relapse in last 12 months: 24 (18.6%) Time since onset: 5.12 yrs (6.68) Percentage diagnosed with Poser criteria: 36 (27.9%) Time since last relapse, of those with last-year relapses: 3.76 mos (2.93) Steroid treatment episodes: 0.50 (0.55) Percentage needing more than one course of steroids: 49 (38.0%)	**Arm 1**: IFN β-1a 44 SC three times weekly (Rebif) **Arm 2**: IFN β-1b 250 µg SC every other day (Betaferon)	**Randomised** 65 arm 1 64 arm 2
REGARD 2008 RRMS (McDonald 2001)	**Country:** Argentina, Austria, Brazil, Canada, France, Germany, Ireland, Italy, Netherlands, Russia, Spain, Switzerland, UK, and USA **No. of countries:** 14 **Centres**: 80 **Study period**: February and December 2004, with 96 weeks follow up **Sponsor**: EMD Serono, Pfizer	**Mean age** 36.8 **Mean sex**: 29.5% male **Race**: 93.6% white **EDSS Score**: 2.34 **Relapse rate**: Presented as distribution of relapses; months since last relapse about 5 on average **Time from diagnosis of MS**: Years since first relapse: 6.2 **Other clinical features of MS**:	**Arm 1**: IFN β-1a 44 SC three times weekly (Rebif) **Arm 2**: GA 20 mg SC daily (Copaxone)	**Randomised** 386 arm 1 378 arm 2

Study ID MS type (diagnostic criteria) Included in TA32?	Study details	Characteristics of participants at baseline	Intervention	Participants
		Receiving steroid treatment in last 6 months: 43.7%		
REMAIN 2012 RRMS/SPMS (diagnostic criteria unclear)	**Country:** Germany **No. of countries:** 1 **Centres**: 9 **Study period**: October 2005-November 2009. 96 weeks follow up **Sponsor**: Merck-Serono	**Mean age** 44.3 (SD 6.7) **Mean sex**: 70% female **Race**: NA **EDSS Score**: Not provided overall; median between 4.0 and 4.3 **Relapse rate**: 26 had no relapses in prior year, 3 had 1 relapse, and 1 had 2 relapses **Time from diagnosis of MS**: NA **Other clinical features of MS**: Time since onset: 12.3 years (7.2) RRMS: 13 (43.3%); SPMS 17 (56.7%)	**Arm 1**: IFN β-1a 44 SC three times weekly (Rebif) **Arm 2**: No treatment; presumably BSC	**Randomised** 15 arm 1 15 arm 2
Schwartz 1997 RRMS (Poser)	**Country:** USA **No. of countries:** 1 **Centres**: Unclear **Study period**: Unclear but 12 months follow up **Sponsor**: Colorado Neurological Institute, Rocky Mountain MS Center, Agency for Health Care Policy and Research	**Mean age** 43.6 **Mean sex**: 77.7% female **Race**: NA **EDSS Score**: NA **Relapse rate**: NA **Time from diagnosis of MS**: 9.2 years **Other clinical features of MS**: NA	**Arm 1**: IFN β-1b 250 µg SC every other day (Betaferon) **Arm 2**: No placebo indicated; likely ongoing BSC	**Randomised** 34 arm 1 45 arm 2
SPECTRIMS 2001 SPMS (Lublin 1996) Included in TA32	**Country:** Canada, Australia, Denmark, France, Netherlands, Sweden, Switzerland, UK **No. of countries:** 8 **Centres**: 22 **Study period**: Not specified. 3 years follow up **Sponsor**: Serono Pharmaceuticals	**Mean age** 42.8 (SD 7.1) **Mean sex**:63% female **Race**: NA **EDSS Score**: mean, SD 5.4 **Relapse rate**: mean, SD 0.9 (1.3) exacerbation in 2 years before study **Time from diagnosis of MS**: 13.3 yrs (SD 7.1) **Other clinical features of MS**: 53% exacerbation-free in last 2 years, average change in EDSS score over last two years 1.6 (0.9), duration of SPMS 4.0 yrs (3.0), SNRS score 63.5 (11.8), ambulation index 3.6 (1.4)	**Arm 1**: IFN β-1a 44 SC three times weekly (Rebif) **Arm 2**: IFN β-1a 22 µg SC three times weekly (Rebif) **Arm 3**: Placebo	**Randomised** 204 arm 1 209 arm 2 205 arm 3

9.3.2 Risk of bias and methodological quality

The risk of bias graphs for all MS types and for each MS type across all included studies are presented in Figure 2. Figure 3 also provides the assessment of risk of bias for each of the included studies.

Risk in randomization or allocation methods

All studies that adequately detailed their method of randomization (21/35) used a method that was judged to be at low risk of bias. Studies that reported methods of allocation concealment (the concealment of study allocation before the beginning of assigned treatment) were also judged to be at low risk of bias (22/35), with the exception of one study that used open allocation (Bornstein 1987[168]). All studies citing central allocation were judged as having a low risk of bias.

Risk in methods of blinding

In the studies examined, 83% (30/35) were at high risk of bias from either complete or partial participant unblinding. In 14 studies, most of which were comparisons between different active drugs, specifically did not blind participants or practitioners, and in another 16 studies, participants were initially blinded, but at high risk of unblinding from increased rates of side effects. In particular, the lack of blinding in comparisons between different drugs meant that risk of bias was imbalanced across different comparisons for the same outcome. We designated all studies in which the rates of side effects (in particular, injection site reactions) in one study group were double that of another to be at high risk of bias from participant unblinding. In the two studies designated as low risk of bias in participant blinding, side effect rates were not increased by a factor of two (one study tested active versus active treatments).

Blinding of outcome assessment was made similarly difficult by injection site reactions. Blinding of outcome assessment was only designated as low risk if injection sites reaction rates were increased by less than a factor of 2 in the treatment group (two studies), or if participants were specifically instructed to cover their injection sites (eight studies). In nine cases, outcome assessors were otherwise blinded but injection sites were not covered, and these studies were designated to be at high risk of bias. Additionally, studies in which participants were unblinded were designated at high risk of bias in outcome assessment, if studies did not report that participants were given specific instructions against sharing treatment information with assessors. All studies that reported MRI outcomes and detailed methods for blinding of MRI assessment were found to be at low risk of bias (13/15).

Risk in data analysis and reporting

29% (10/35) of studies were found to be at high risk of bias from missing data, based on large amounts of missing data, difference in rates of loss to follow-up between arms, or lack of reporting of imputation methods. In 17% (6/35) of studies outcomes were not reported as stated, and these were designated to be at high risk of bias from selective reporting. Finally, all studies funded by drug manufacturers were designated as high risk of bias under the ‘other’ category, as this was not covered by other questions in the risk of bias tool.

Figure 2: Risk of bias by MS type

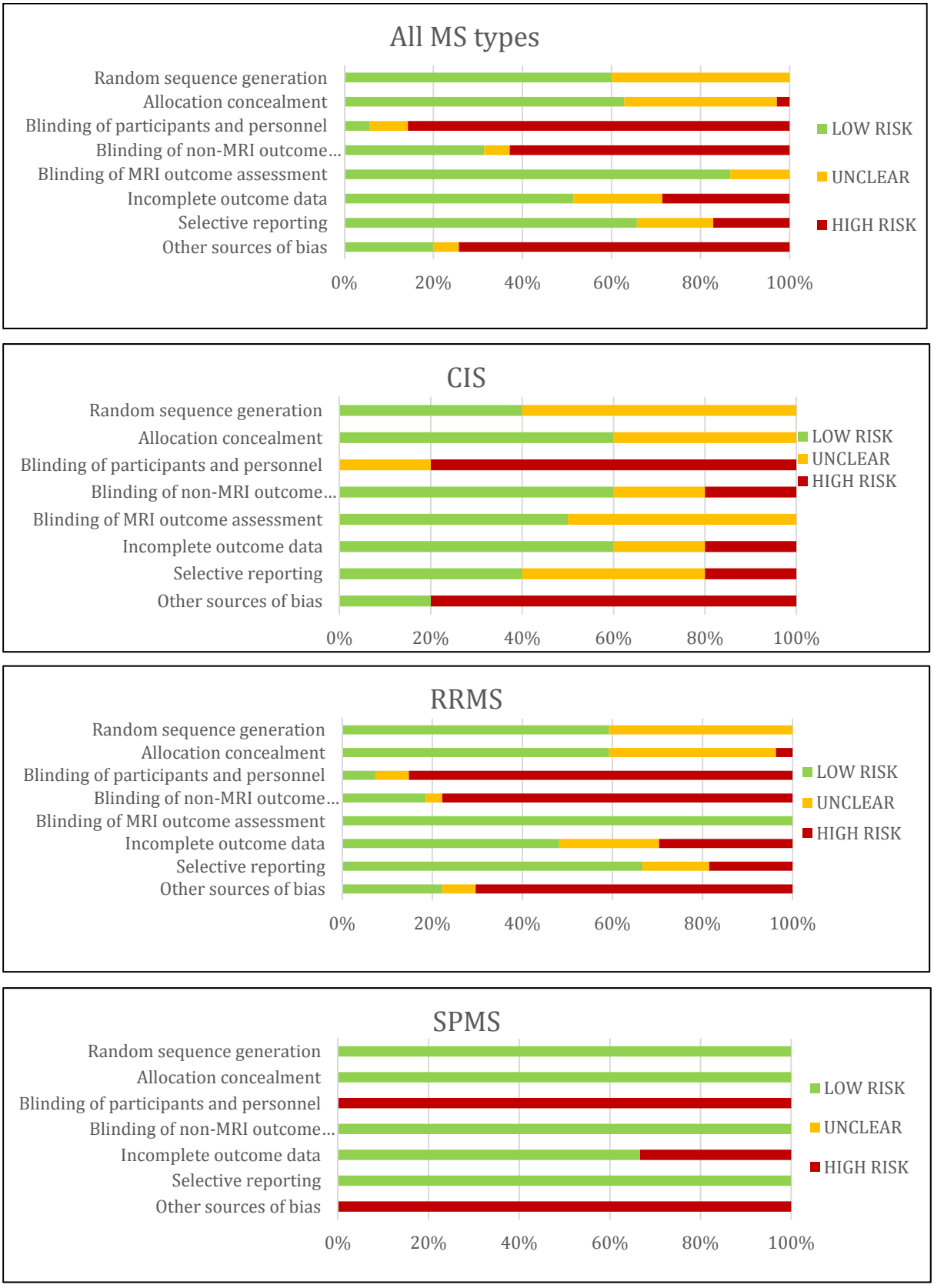


Figure 3: Risk of bias by study

MS type	Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment (except MRI)	Blinding of MRI outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
CIS	BENEFIT 2006	?	+	-	+	+	+	?	-
CIS	CHAMPS 2000	?	?	-	+	+	?	+	-
CIS	Pakdaman 2007	?	?	?	?	N/A	-	-	-
CIS	PreCISe 2009	+	+	-	-	?	+	+	+
CIS	REFLEX 2012	+	+	-	+	?	+	?	-
RRMS	ADVANCE 2014	+	+	-	-	+	-	+	-
RRMS	AVANTAGE 2014	?	?	-	-	N/A	?	+	+
RRMS	BECOME 2009	?	?	-	-	+	+	+	-
RRMS	BEYOND 2009	+	+	-	-	N/A	?	+	-
RRMS	Bornstein 1987	?	-	-	-	N/A	+	+	+
RRMS	BRAVO 2014	+	+	-	+	N/A	+	-	-
RRMS	Calabrese 2012	+	+	-	-	+	+	-	+
RRMS	CombiRx 2013	+	+	+	+	N/A	-	+	+
RRMS	CONFIRM 2012	+	+	-	-	+	-	+	-
RRMS	Cop1 MSSG 1995	?	+	-	-	N/A	+	+	+
RRMS	ECGASG 2001	+	+	-	-	+	+	?	-
RRMS	Etemadifar 2006	?	?	-	-	N/A	+	?	?
RRMS	EVIDENCE 2007	+	+	-	-	N/A	+	+	-
RRMS	GALA 2013	?	+	-	-	+	?	+	-
RRMS	GATE 2015	+	+	-	-	+	+	+	-
RRMS	IFNB MSSG 1995	?	?	-	-	+	-	+	-

MS type	Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment (except MRI)	Blinding of MRI outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
RRMS	IMPROVE 2012					N/A			
RRMS	INCOMIN 2002								
RRMS	Kappos 2011								
RRMS	Knobler 1993					N/A			
RRMS	Mokhber 2014					N/A			
RRMS	MSCRG 1996								
RRMS	PRISMS 1998					N/A			
RRMS	REFORMS 2012					N/A			
RRMS	REGARD 2008					N/A			
RRMS	REMAIN 2012					N/A			
RRMS	Schwartz 1997					N/A			
SPMS	ESG 1998					N/A			
SPMS	NASG 2004					N/A			
SPMS	SPECTRIMS 2001					N/A			

9.3.3 Summary: study characteristics and risk of bias

We located 35 primary studies from a variety of settings and covering all the drugs listed in the NICE scope. These studies were of variable quality, with particular issues posed by risk of unblinding of patients and outcome assessors due to injection site reactions, as well as imbalanced risk of bias from open-label comparisons. Many studies were sponsored by manufacturers, and most studies were at high risk of bias due to missing data.

9.4 *Clinical effectiveness: clinically isolated syndrome*

Our analysis was informed by five included trials: BENEFIT 2006,[169] CHAMPS 2000,[170] Pakdaman 2007,[171] PreCISe 2009[172] and REFLEX 2012.[173] It should be noted that trialists generally examined time to 'clinically

definite MS', defined using Poser criteria and involving a second relapse or neurological deterioration, though some also presented analyses examining time to 'McDonald MS', in which MRI findings could be used with clinical findings to arrive at a diagnosis.

9.4.1 IFN β-1a 30 µg IM once a week (Avonex) vs. placebo

Two trials evaluated IFN β-1a 30 µg IM once a week, both against placebo: CHAMPS 2000[170] and Pakdaman 2007.[171]

Time to diagnosis of MS

Both studies reported significant differences in favour of IFN β-1a in delaying time to confirmation of clinically definite MS, diagnosed generally by a second relapse, but in some cases by progressive neurological deterioration. CHAMPS 2000,[170] which followed up 393 patients up to three years, found a reduction in hazard of more than half (HR=0.49, 95% CI [0.33, 0.73]). Pakdaman 2007,[171] which followed up 202 patients up to three years, found a reduction in conversion to clinically definite MS (incidence 36.6% vs. 58.2%). We converted this to a hazard ratio of 0.54 (0.36, 0.81).

In separate publications, CHAMPS 2000 also presented analyses stratified by risk levels, site of first lesion[174] and type of first attack.[175] In analyses comparing patients with monofocal and multifocal disease at first demyelinating event,[175] patients with monofocal disease had a similar reduction in hazard to the whole trial population (HR=0.45, 95% CI [0.27, 0.74]) while patients with multifocal disease had a decreased reduction in hazard (0.64, [0.32, 1.28]).

Freedom from disease activity

CHAMPS 2000[174] evaluated freedom from disease activity via several composite outcomes, each of which showed a reduction in hazard associated with IFN β-1a. Patients receiving IFN β-1a were less likely to have a composite outcome of clinically definite MS or more than one new or enlarging T2 lesion, though this outcome may be closer to McDonald MS (adjusted HR 0.47, 95% CI [0.36, 0.62]); of clinically definite MS or at least one new or enlarging T2 lesion (0.55, [0.42, 0.71]); or of either clinically definite MS, at least one new or enlarging T2 lesion, or at least one gadolinium-enhancing lesion (0.60, [0.47, 0.78]).

Adverse events and mortality

Full results are available on request. Mortality was not reported in these studies.

9.4.2 IFN β-1a 44 µg SC three times a week (Rebif) vs. placebo

One trial evaluated IFN β-1a 44 µg SC three times a week against placebo: REFLEX 2012. [173] (This trial also included an arm testing IFN β-1a 44 µg SC once a week which we will not consider further here as it is not covered by the recommended posology).

Time to diagnosis of MS

In REFLEX 2012,[173] 340 patients in the relevant trial arms were followed for up to two years, and a significant reduction in hazard for conversion to clinically definite MS was found (HR 0.48, 95% CI [0.31, 0.73]). An additional analysis examined time to conversion to McDonald MS (i.e. using MRI criteria as well) and found a similar reduction in hazard (0.49, [0.38, 0.64]), corresponding to a difference in median days to diagnosis of 310 vs. 97.

Several subgroup analyses were undertaken on the study sample by risk level, and key findings from Freedman and colleagues[176] are summarised here. In examining time to clinically definite MS, patients with monofocal presentation (HR 0.58, 95% CI [0.40, 0.84]) and with multifocal presentation (0.45, [0.31, 0.64]) both experienced decreased hazard of conversion to clinically definite MS, but type of presentation did not appear to be a significant moderator. Similarly, an analysis that 're-diagnosed' patients as having McDonald MS or not based on the revised 2010 criteria found that patients who were McDonald 2010 MS negative had a significantly decreased hazard of conversion to McDonald 2005 MS (HR 0.49, $p<0.001$), as did those who were McDonald 2010 MS positive at baseline (0.54, $p=0.01$).

Adverse events and mortality

Full results are available on request. Mortality was not significantly different between the groups, though no events occurred in the study drug arm and two deaths occurred in the placebo arm.

9.4.3 IFN β-1b 250 µg SC every other day (Betaferon/Extavia) vs. placebo

One trial evaluated IFN β-1b 250 µg SC every other day against placebo: BENEFIT 2006.[169]

Time to diagnosis of MS

In BENEFIT 2006,[169] 468 patients were followed for up to two years. The study drug delayed time to clinically definite MS (HR=0.50, 95% CI [0.36, 0.70]). This reduction in hazard corresponded to a difference in days to diagnosis of 618 vs. 255 at the 25th percentile. Trialists also considered time to McDonald MS, an effect that was similar in magnitude (0.54, [0.43, 0.67]).

BENEFIT 2006 also presented analyses stratified by risk levels, site of first lesion and type of first attack.[177] In analyses comparing patients with monofocal and multifocal disease at first demyelinating event, patients with monofocal disease had a similar reduction in hazard to the whole trial population (HR=0.45, 95% CI [0.29, 0.71]) while patients with multifocal disease had a decreased reduction in hazard (0.63, [0.40, 0.99]).

MS symptoms and health-related quality of life

Patients in BENEFIT 2006 were assessed for cognitive performance using the paced auditory serial addition test (PASAT-3").[178] At year 2, patients receiving the study drug had greater increases in score on this test than patients receiving placebo, including under conservative assumptions (2.0 vs 0.6, $p=0.021$). Additionally, patient-reported physical health and health-related quality of life data were collected in this trial.[169] Scores were not different between groups and were stable over the trial.

Adverse events and mortality

Full results are available on request. No deaths were reported in BENEFIT 2006.[169]

9.4.4 GA 20 mg SC once daily (Copaxone) vs. placebo

One trial evaluated GA 20 mg SC once daily against placebo: PreCISe 2009.[172]

Time to diagnosis of MS

PreCISe 2009[172] followed up 481 patients for up to three years, though the trial was stopped early for benefit. Participants receiving GA 20 mg SC once daily had reduced hazard of conversion to clinically definite MS (HR=0.55, 95% CI [0.4, 0.77]), though clinically definite MS was defined here as the occurrence of a second exacerbation. The corresponding difference in days to diagnosis was 722 vs. 336 at the 25th percentile.

Adverse events and mortality

Full results are available on request. Mortality was not significantly different between groups, although PreCISe 2009[172] reported only one death, in the study drug arm.

9.4.5 Meta-analyses: time to clinically definite MS

Pairwise meta-analyses

Direct evidence from comparisons is shown in Figure 4. All comparisons were against placebo. Only one comparison, IFN β-1a 30 μg IM once a week vs. placebo, included more than one study. The pooled effect size suggested that IFN β-1a 30 μg IM once a week reduces time to clinically definite MS (HR=0.52, 95% CI [0.39, 0.68]), with low heterogeneity (I2=0%, p=0.718).

Network meta-analysis

The set of studies reporting hazard ratios for time to clinically definite MS formed a connected network (see Figure 12). This network was star-shaped, meaning it contained no comparisons between active drugs. We estimated this model using random effects as per the protocol.

Rankings from the network meta-analysis suggested that IFN β-1a 44 μg SC thrice weekly was ranked best, followed by IFN β-1b 250 μg SC every other day, IFN β-1a 30 μg IM once a week and GA 20 mg SC once daily (see Table 5). Placebo was ranked last.

Figure 4: Pairwise meta-analyses, time to clinically definite MS

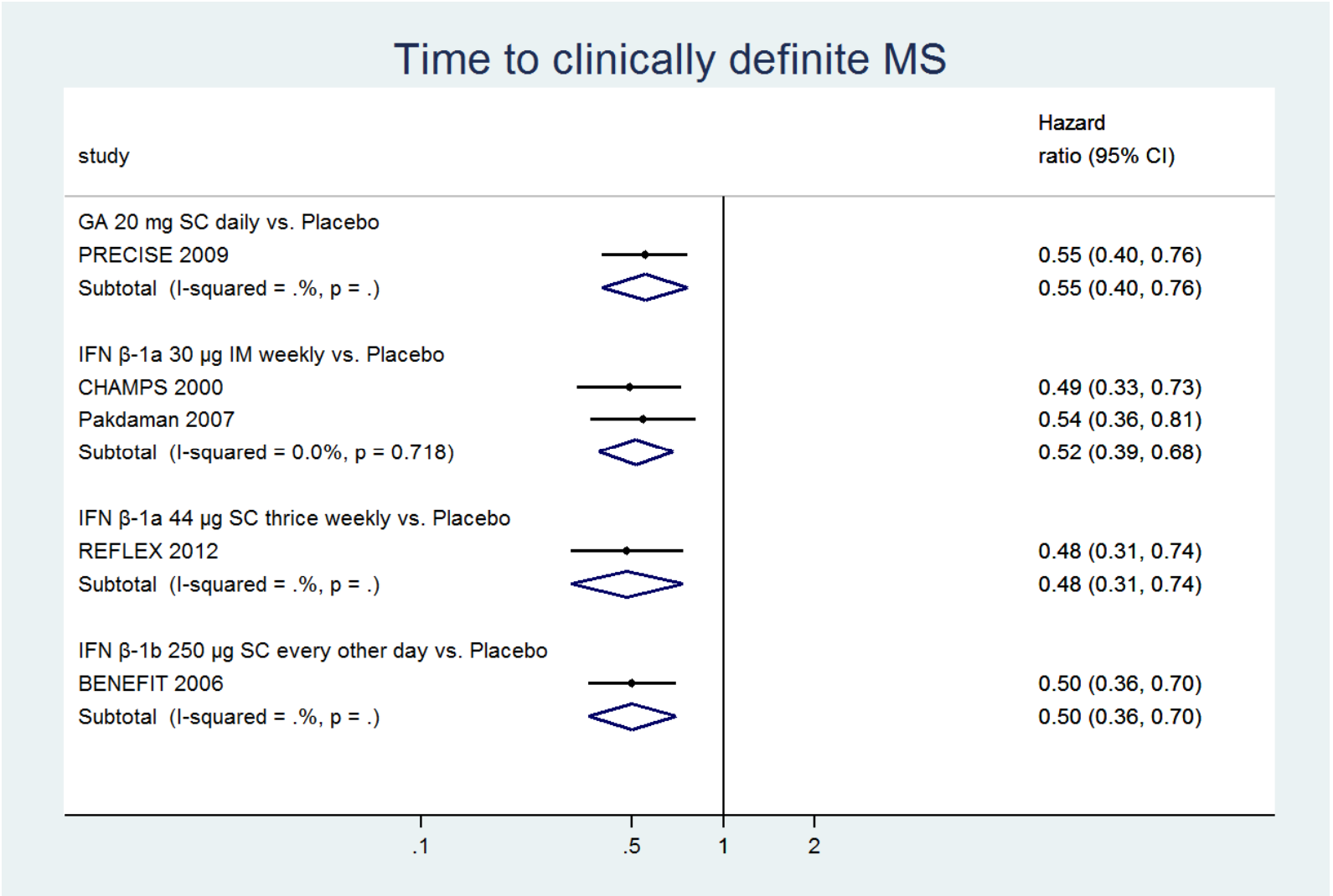
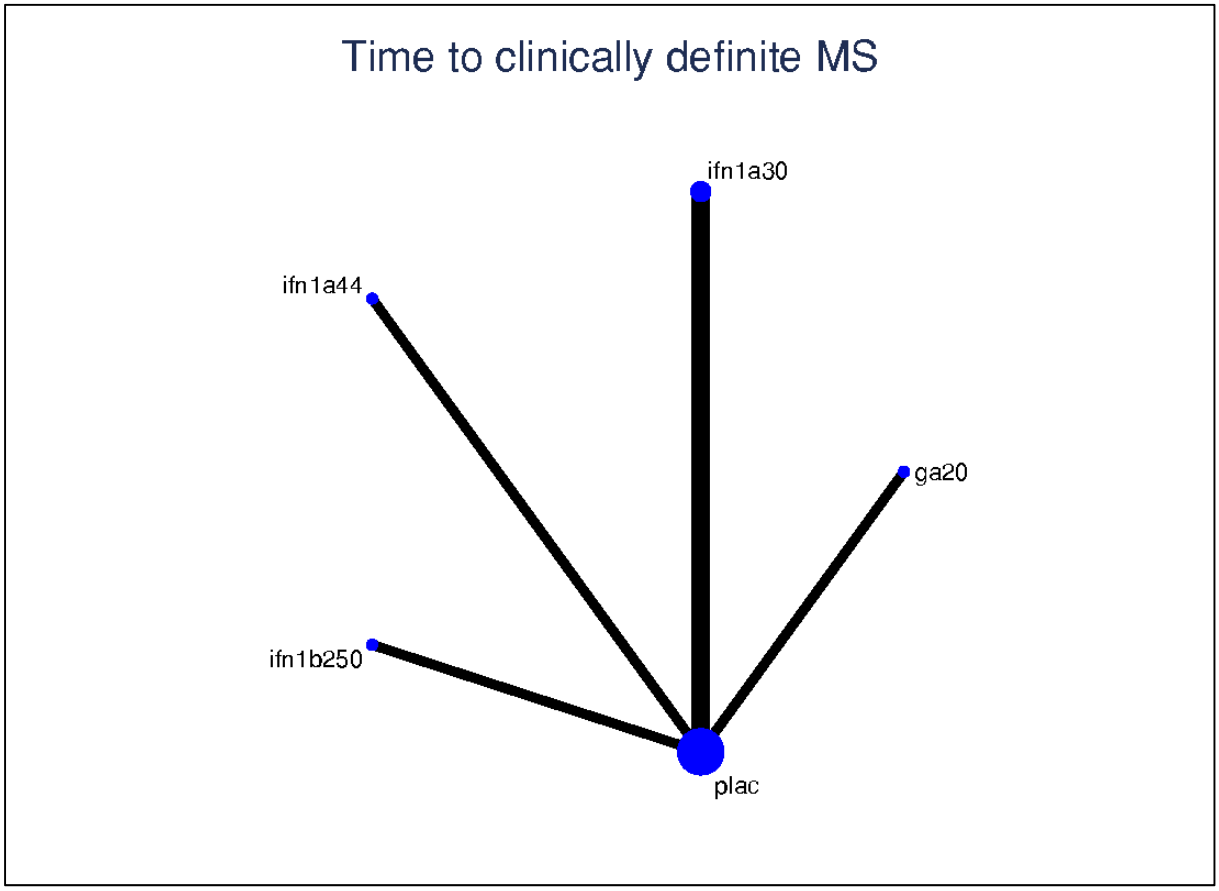


Figure 5: Network of studies, time to clinically definite MS

ifn1a30: IFN β-1a 30 µg IM once a week; ifn1a44: IFN β-1a 44 µg SC three times weekly; ifn1b250: IFN β-1b 250 µg SC every other day; ga20: GA 20 mg SC once daily; plac: placebo



Findings for comparisons between active drugs against placebo were identical, as expected, to those in the pairwise meta-analyses. Findings for indirect comparisons between drugs did not suggest superiority of any one drug over another.

Because the network was star-shaped, we could not test for inconsistency.

Sensitivity analysis

We also re-estimated the network with effect sizes for time to conversion to McDonald MS for those studies reporting it. Effectiveness estimates were robust to this change.

9.4.6 Meta-analyses: not possible for adverse events in CIS

Of the four studies (PreCISe 2009,[172] REFLEX 2012,[173] CHAMPS 2000,[170] BENEFIT 2006[169]) reporting discontinuations due to adverse events, two studies reported discontinuations over 36 months (PreCISe 2009, CHAMPS 2000) and two reported discontinuations over 24 months (REFLEX 2012 and BENEFIT 2006). As a result, we did not estimate a network meta-analysis for discontinuations in CIS. Estimates can be found in Table 6.

Table 5: Network meta-analysis: time to clinically definite MS

Findings are expressed as HR (95% CI).

Drug	SUCRA	IFN β-1a 44 µg SC thrice weekly	IFN β-1b 250 µg SC every other day	IFN β-1a 30 µg IM weekly	Glatiramer 20 mg daily	Placebo
IFN β-1a 44 µg SC thrice weekly	0.70		0.96 (0.56, 1.65)	0.93 (0.56, 1.55)	0.87 (0.51, 1.50)	0.48 (0.31, 0.74)
IFN β-1b 250 µg SC every other day	0.68			0.97 (0.63, 1.50)	0.91 (0.57, 1.45)	0.50 (0.36, 0.70)
IFN β-1a 30 µg IM weekly	0.62				0.94 (0.61, 1.45)	0.52 (0.39, 0.68)
Glatiramer 20 mg daily	0.5					0.55 (0.40, 0.76)
Placebo	0					

Table 6: Discontinuation due to AEs in CIS studies

Study	Comparison	Follow-up (months)	Treatment arm events	Treatment group	Treatment events proportion	Placebo arm events	Placebo group	Placebo events proportion
PreCISe 2009	GA 20 mg daily vs. Placebo	36	14	243	5.8%	4	238	1.7%
REFLEX 2012	IFN β-1a 44 µg SC thrice weekly vs. Placebo	24	5	171	2.9%	6	171	3.5%
CHAMPS 2000	IFN β-1a 30 µg IM weekly vs. Placebo	36	1	193	0.5%	7	190	3.7%
BENEFIT 2006	IFN β-1b 250 µg SC every other day vs. Placebo	24	24	292	8.2%	1	176	0.6%

9.4.7 Summary: clinically isolated syndrome

Comparisons for included drugs all relied on one or two trials, but each comparison suggested that that IFN or GA delayed time to clinically definite MS over a two to three year follow-up. This finding appeared to be robust to the diagnostic criteria used to establish a definitive MS diagnosis. The network meta-analysis did not suggest the superiority of one drug over another. Adverse events tended to be higher in trial arms receiving the active drugs, though where mortality was reported, it was not significantly higher in patients receiving the study drug. Findings on additional outcomes (MS symptoms, health-related quality of life) were infrequently reported.

9.5 *Clinical effectiveness: relapsing remitting MS*

Our analysis was informed by 27 trials. Of these 27 trials, one evaluated health-related quality of life measures alone (Schwartz 1997[179]) and one evaluated adverse effects alone (AVANTAGE 2014[180]). In addition, two trials reported on mixed populations: REMAIN 2012[181] and BECOME 2009.[182] REMAIN 2012,[181] which followed up 30 participants over 96 weeks, included a mixed RRMS (n=13) and SPMS (n=17) population. Because of the size of this open-label trial, because data were not stratified by type of MS and because treatment switching was allowed, we decided to include this trial in narrative synthesis but not in meta-analyses. In contrast, BECOME 2009,[182] which followed up 75 participants over two years, included 14 patients diagnosed with CIS before the revision of the McDonald criteria. Because we judged it likely that many of the 14 patients originally diagnosed as having CIS would have been classed as having RRMS under the most recent criteria, we analysed this trial alongside other RRMS-only trials. Thus, 24 relevant trials reported key clinical outcomes.

Several characteristics of the 'epidemiology' of the trial network bear discussing first: design of included multiarm trials, two-arm trials comparing active drugs against each other and trials with mixed populations. Of the 25 trials reporting clinical outcomes, four trials had three relevant treatment arms:

- both Etemadifar 2006[183] and Mokhber 2014[184, 185] evaluated a) IFN β-1a 44 µg SC three times a week against b) IFN β-1a 30 µg IM once a week against c) IFN β-1b 250 µg SC every other day;
- Calabrese 2012[186] evaluated a) IFN β-1a 44 µg SC three times a week against b) IFN β-1a 30 µg IM once a week against c) GA 20 mg SC once daily; and
- PRISMS 1998[187] compared IFN β-1a 44 µg SC three times a week against b) IFN β-1a 22 µg SC three times a week against c) placebo.

An additional seven two-arm trials compared active drugs against each other:

- two trials, BECOME 2009[182] and BEYOND 2009,[188] compared IFN β-1b 250 µg SC every other day against GA 20 mg SC once daily;
- CombiRx 2013[189] compared IFN β-1a 30 µg IM once a week against GA 20 mg SC once daily; and
- REGARD 2008[190] compared IFN β-1a 44 µg SC three times a week against GA 20 mg SC once daily.
- EVIDENCE 2007[191-193] compared IFN β-1a 44 µg SC three times a week against IFN β-1a 30 µg I M once a week;
- INCOMIN 2002[194] compared IFN β-1b 250 µg SC every other day against IFN β-1a 30 µg IM once a week; and

- REFORMS 2012[195] compared IFN β-1a 44 µg SC three times a week against IFN β-1b 250 µg SC every other day.

9.5.1 IFN β-1a 30 µg IM once a week (Avonex) vs. placebo

Our analysis was informed by three trials comparing IFN β-1a 30 µg IM once a week against placebo: BRAVO 2014,[196] Kappos 2011[197] and Multiple Sclerosis Collaborative Research Group 1996 (referred to as MSCRG 1996[198]). BRAVO 2014[196] was designed as a trial to compare oral laquinimod against IFN β-1a 30 µg IM once a week and oral placebo, while Kappos 2011[197] compared intravenous ocrelizumab against IFN β-1a 30 µg IM once a week and intravenous placebo. MSCRG 1996[198] compared IFN β-1a 30 µg IM once a week against an IM placebo.

An additional six trials compared IFN β-1a 30 µg IM once a week against other drugs: three multi-arm trials (Calabrese 2012,[186] Etemadifar 2006,[183] Mokhber 2014[184, 185]) and three two-arm trials (CombiRx 2013,[189] EVIDENCE 2007[191-193] and INCOMIN 2002[194]).

Relapse outcomes

Findings on relapse outcomes relied on three trials with different follow-up, including two of the largest trials in this review. All three studies suggested a beneficial effect of IFN β-1a 30 µg IM once a week in reducing the rate of relapses. BRAVO 2014,[196] which followed 887 patients in the relevant trial arms for 24 months, found that patients receiving IFN β-1a 30 µg IM once a week had a 26% reduction in the ARR (RR=0.74, 95% CI [0.60, 0.92]). In Kappos 2011,[197] 108 patients were followed up over 24 weeks, and while ARR was lower in patients receiving I FN β-1a 30 µg IM once a week (ARR=0.36, 95% CI [0.22, 0.60]) than in patients receiving placebo (ARR=0.64, 95% CI [0.43, 0.94]), this difference was only marginally significant (p=0.07). Finally, in MSCRG 1996,[198] 301 patients were followed up for up to three years, though the study was stopped early for efficacy and thus patients had variable time to follow-up. In analyses including all patients, the ARR for patients receiving the study drug was significantly less than the ARR for patients receiving placebo (0.67 vs. 0.82, p=0.04).

Only MSCRG 1996[198] reported time to first relapse. This was not presented with an estimate of a hazard ratio, but a log rank test suggested that IFN β-1a 30 µg IM once a week did not significantly delay time to first exacerbation as compared to placebo (median weeks 47.3 vs. 36.1, p=0.34).

Finally, the three studies reported findings for proportion relapse-free, though findings were somewhat heterogeneous and comparability is limited by differential follow-up. BRAVO 2014[196] found that 69% of patients receiving IFN β-1a 30 µg IM once a week were relapse free, as compared to 61% of patients receiving placebo (p=0.023). This difference was narrower in Kappos 2011[197] (IFN β-1a 30 µg IM once a week 78% vs. placebo 76%), with risk ratio for experiencing any relapses of 0.92 (95% CI [0.46, 1.84]). MSCRG 1996[198] only reported proportions for those patients with the intended 104 weeks on study, excluding those enrolled but who did not complete the 104 weeks before the study was stopped. For the 85 patients included who received

IFN β-1a 30 µg IM once a week, 38% were free of relapses, as opposed to 26% of the 87 patients receiving placebo. A significance test was not presented.

Relapse severity

We could not locate any relevant comparisons between IFN β-1a 30 µg IM once a week and placebo on outcomes relating to moderate or severe relapses or steroid-treated relapses.

Disability progression

Only BRAVO 2014[196] estimated time to disability progression confirmed at 3 months. Patients receiving IFN β-1a 30 µg IM once a week and placebo were delayed, but not significantly so, in time to progression (HR=0.74, 95% CI [0.51, 1.09]). Results for disability progression confirmed at 6 months were similar (0.73, [0.47, 1.14]). MSCRG 1996[198] also reported time to progression confirmed at 6 months. Based on a Kaplan-Meier analysis, predicted probability of progression at 2 years was 21.9% in patients receiving IFN β-1a 30 µg IM once a week as compared to 34.9% in patients receiving placebo (log rank p=0.02), indicating a slowing of time to progression[198, 199]. In a separate publication, the reduction in hazard was reported as 43.0% (i.e. HR=0.570, p=0.03)[200].

Empirical proportions of patients with progression confirmed at 3 months were also reported by BRAVO 2014[196] (IFN β-1a 30 µg IM once a week 11% vs. placebo 13%). Proportion progression at 6 months was similarly low (IFN β-1a 30 µg IM once a week 8% vs. placebo 10%). In MSCRG 1996, empirical proportions for patients with progression confirmed at 6 months were reported for the full sample in a publication separate to the main study report[200]. Patients receiving IFN β-1a 30 µg IM once a week had a lower probability of progression than patients receiving placebo (15% vs. 25%), though follow-up was variable. Significance tests were not presented for these proportions *per se* (i.e. not as part of survival analysis, discussed above) by any of the three trials.

Magnitude of change from baseline in EDSS score was only presented by MSCRG 1996.[198] In patients completing 104 weeks on study, patients receiving IFN β-1a 30 µg IM once a week had lesser increase in EDSS as compared to patients receiving placebo (0.25 vs. 0.74, p=0.02). This finding was similar in patients examined to week 130, in which the lower of the scores at week 104 or week 130 were taken as a measure of 'sustained' change (0.02 vs. 0.61, p=0.02). In BRAVO 2014,[196] patients receiving IFN β-1a 30 µg IM once a week had a lesser decrease in the Multiple Sclerosis Functional Composite at 24 months, but this difference was not significant (z-scores -0.045 vs. -0.14, p=0.21).

Freedom from disease activity

We could not locate any relevant comparisons between IFN β-1a 30 µg IM once a week and placebo on combined clinical-MRI outcomes for freedom from disease activity.

MS symptoms and health-related quality of life

MSCRG 1996[201] reported performance on both the Comprehensive and Brief Neuropsychological Batteries by examining change from baseline to two years, and estimated models with both no covariates and with baseline performance as a covariate. While exact effect sizes were not provided, the study found that in patients completing 104 weeks on study and as compared to placebo, IFN β-1a 30 µg IM once a week improved information processing and memory (p=0.036 unadjusted, p=0.011 adjusted) and visuospatial abilities and executive functions (p=0.005 unadjusted, p=0.085 adjusted), but not verbal abilities and attention span (p=0.603 unadjusted, p=0.917 adjusted). Findings were similar for the Brief Neuropsychological Battery (p=0.020 for both unadjusted and adjusted), though IFN β-1a 30 µg IM once a week did not significantly delay time to onset of deterioration confirmed at 6 months (log rank p=0.094). Analyses of the PASAT indicated that while the difference in magnitude of change did not rise to significance (p=0.119 unadjusted, p=0.090 adjusted), patients receiving IFN β-1a 30 µg IM once a week did delay time to sustained deterioration (log rank p=0.023).

Additionally, patients receiving IFN β-1a 30 µg IM once a week had decreased hazard of sustained worsening in the timed 25-foot walk (HR=0.401, p=0.04). However this decreased hazard was not evidenced in the nine-hole peg test with dominant hand (HR=0.514, p=0.07) or non-dominant hand (HR=0.494, p=0.10), or the box and block test in the dominant hand (HR=0.581, p=0.45) or non-dominant hand (HR=0.835, p=0.75).[200] Investigators also tested a variety of combinations of these endpoints. In a separate publication, use of an instrument to examine functional independence showed that change over 104 weeks in cognitive aspects of functional independence was not significant. This was the case both when considered as difference in means (p=0.08) and in time to sustained worsening (log rank p=0.188), with similar findings for difference in means in motor aspects of functional independence (p=0.10, log rank p=0.368).[202] Total changes in functional independence were significant at 104 weeks (p=0.03).

Finally, MSCRG 1996 reported on effects on the Sickness Impact Profile as a measure of quality of life.[203] In the study population as a whole, there were no differences between placebo and the study drug on the overall measure, nor on its physical or psychosocial components. However, when considering patients with low health-related quality of life at baseline (defined as a score greater than or equal to 10 on the measure), patients receiving the study drug had a greater improvement on physical aspects of the measure (-3.78 vs. 3.57, p<0.05).

Adverse events and mortality

We stratified comparison of AEs by type of placebo, as local AEs (e.g. injection site reactions) would not apply in studies with oral or intravenous placebos. Full results are available on request.

Mortality was not different between groups for either type of placebo. However, only one death occurred in MSCRG 1996[198] (in the study drug arm), no deaths occurred in Kappos 2011,[197] and only one death occurred in BRAVO 2014[196] (in the study drug arm).

Summary of the narrative synthesis: IFN β-1a 30 µg IM once a week (Avonex) vs. placebo

Findings from three trials suggested that relative to placebo, IFN β-1a 30 µg IM once a week reduces relapse rate, though findings were less clear for other relapse-related outcomes. Findings from two trials suggested that IFN β-1a 30 µg IM once a week also has a beneficial effect in delaying disability progression, though only MSRCG 1996[198] presented significant results. Findings from MSCRG 1996[198-202] on MS symptoms were inconsistent across tests. We were unable to find any relevant comparisons for relapse severity, defined as moderate/severe or steroid-treated relapses, or combined clinical-MRI measures of freedom from disease activity. Mortality was rare and not significantly different between groups.

9.5.2 IFN β-1a 30 µg IM once a week (Avonex) vs. IFN β-1a 44 µg SC three times a week (Rebif)

Four trials compared IFN β-1a 30 µg IM once a week against IFN β-1a 44 µg SC three times a week: Calabrese 2012,[186] Etemadifar 2006,[183] EVIDENCE 2007[191-193] and Mokhber 2014.[184, 185]

Relapse outcomes

Findings for relapse outcomes relied on three trials, of which EVIDENCE 2007[191-193] was the largest by far. Calabrese 2012[186] analysed 141 patients randomised to either IFN β-1a 30 µg IM once a week (n=47), IFN β-1a 44 µg SC three times a week (n=46) or GA 20 mg SC once daily (n=48) over two years with complete follow-up for analysed patients. Relapses were apparently analysed using a normal distribution, though formal significance tests were not presented. At two years, patients receiving IFN β-1a 30 µg IM once a week had an average ARR of 0.5 (SD=0.6) while patients receiving IFN β-1a 44 µg SC three times a week had an average ARR of 0.4 (SD=0.6). We estimated a rate ratio of 1.25 (95% CI [0.81, 1.92]). Etemadifar 2006[183] analysed 90 patients randomised 1:1:1 to either IFN β-1a 30 µg IM once a week, IFN β-1a 44 µg SC three times a week or IFN β-1b 250 µg SC every other day. Because relapses were analysed using a repeated measures ANOVA method with normal distributions, we re-estimated rate ratios based on number of relapses in each arm. Based on a total of 57 relapses in patients receiving IFN β-1a 30 µg IM once a week and 66 relapses in patients receiving IFN β-1a 44 µg SC three times a week, we estimated a rate ratio of 0.86 (95% 0.61, 1.23). Finally, EVIDENCE 2007[192, 193] randomised 677 patients and followed them up for an intended period of at least 48 weeks, with median follow-up of 64 weeks. Patients receiving IFN β-1a 30 µg IM once a week had a higher ARR (0.65) than patients receiving IFN β-1a 44 µg SC three times a week (0.54), which was a statistically significant difference (RR=1.20, p=0.033).

Only EVIDENCE 2007[192, 193] presented data for time to first relapse. The 40th percentile of patients receiving IFN β-1a 30 µg IM once a week had their first relapse at 6.7 months, as opposed to the 40th percentile of patients receiving IFN β-1a 44 µg SC three times a week, who had their first relapse at 13.5 months. Relative to patients receiving IFN β-1a 30 µg IM once a week, patients receiving IFN β-1a 44 µg SC three times a week had decreased hazard of first relapse (HR=0.70, 95% CI [0.56, 0.88]).

Both studies presenting data on proportions of patients free of relapse were in agreement on the direction of effect. In Etemadifar 2006,[183] patients receiving IFN β-1a 30 µg IM once a week were less likely to be free of

relapses than patients receiving IFN β-1a 44 µg SC three times a week (20.0% vs. 56.7%), but a pairwise significance test was not presented. In EVIDENCE 2007,[192, 193] patients receiving IFN β-1a 30 µg IM once a week were less likely to be relapse-free (48%) than patients receiving IFN β-1a 44 µg SC three times a week (56%). That is, the OR for being relapse free at the study's end favoured patients receiving IFN β-1a 44 µg SC three times a week (OR=1.5, 95% CI [1.1, 2.0]).

Relapse severity

Only EVIDENCE 2007[192, 193] reported outcomes related to relapse severity; in this case, ARR for steroid-treated relapses. Patients receiving IFN β-1a 30 µg IM once a week had an ARR for steroid-treated relapses of 0.28, as compared to 0.19 in patients receiving IFN β-1a 44 µg SC three times a week. Thus, the rate ratio for steroid-treated relapses is 1.47 (p=0.009).

Disability progression

Only EVIDENCE 2007[191] reported time to disability progression and proportion of patients progressing. Drawing from interim data on all patients at 48 weeks of follow-up, patients receiving IFN β-1a 30 µg IM once a week appeared to progress faster than patients receiving IFN β-1a 44 µg SC three times a week. However this finding was not significant for either progression confirmed at 3 months (44 µg SC vs. 30 µg IM: HR=0.87, 95% CI [0.58, 1.31]) or progression confirmed at 6 months (HR=0.70, 95% CI [0.39, 1.25]). At end of study, there was no statistical difference in the proportion of patients with disability progression confirmed at three months between those receiving IFN β-1a 30 µg IM once a week and those receiving IFN β-1a 44 µg SC three times a week (17% vs. 16%, p=0.710).

In Calabrese 2012,[186] magnitude of EDSS change did not appear to be numerically different in IFN β-1a 30 µg IM once a week (0.2, SD=0.4) as compared to IFN β-1a 44 µg SC three times a week (0.2, SD=0.5) but formal significance testing was not reported. However, in Etemadifar 2006,[183] patients receiving IFN β-1a 30 µg IM once a week reduced EDSS score by 0.1 (95% CI [-0.2, 0.5]), a numerically smaller decrease than patients receiving IFN β-1a 44 µg SC three times a week (0.3, [0.03, 0.5]). Again, formal significance testing was not reported. Finally, Mokhber 2014[184, 185] found no difference between baseline and 12-month follow-up on EDSS score for IFN β-1a 30 µg IM once a week (0.0, n=20, p=0.548), though a test for change was significant for IFN β-1a 44 µg SC three times a week (-1.0, n=21, p=0.001). Pairwise testing was not performed but an overall test was not significant.

Freedom from disease activity

We could not locate any relevant comparisons between IFN β-1a 30 µg IM once a week and IFN β-1a 44 µg SC three times a week on combined clinical-MRI outcomes for freedom from disease activity.

MS symptoms and health-related quality of life

Mokhber 2014[184] presented tests of cognitive function, though without pairwise comparisons. On all tests presented (selective reminding test, spatial recall test, symbol digit modalities test, PASAT and word list

generation), comparisons across all three treatment groups were not statistically significant except for the symbol digit modalities test. Post hoc tests found evidence that patients receiving IFN β-1a 30 µg IM once a week did not improve as much as patients receiving IFN β-1a 44 µg SC three times a week on the word list generation and PASAT-easy tests.

Additionally, Mokhber 2014[185] disaggregated the MS Quality of Life-54 scale into its subcomponents, including mental health (five components) and physical health (eight components). There were few significant within-groups differences in this small trial, and pairwise significance tests, as well as estimates of change from baseline, were not presented in a standard format, permitting only discussion of direction and significance of differences. Patients receiving IFN β-1a 30 µg IM once a week significantly worsened in energy and fatigue as compared to patients receiving IFN β-1a 44 µg SC three times a week, who improved. However, patients receiving IFN β-1a 30 µg IM once a week significantly improved in experience of physical role limitations as compared to patients receiving IFN β-1a 44 µg SC three times a week, who also improved. Patients receiving IFN β-1a 30 µg IM once a week also significantly improved in both experience of emotional role limitations and cognitive function as compared to patients receiving IFN β-1a 44 µg SC three times a week. Differences were not significant for physical function, health perceptions, pain, sexual function, social function, health distress, overall quality of life or emotional wellbeing.

Adverse events and mortality

Only EVIDENCE 2007[204] reported AEs. No studies reported mortality. Full results are available on request.

Summary of the narrative synthesis: IFN β-1a 30 µg IM once a week (Avonex) vs. IFN β-1a 44 µg SC three times a week (Rebif)

Findings from three trials, of which one was considerably larger than the others, suggested that IFN β-1a 30 µg IM once a week was less effective than IFN β-1a 44 µg SC three times a week on reducing and delaying relapses. Findings from EVIDENCE 2007[192, 193] suggested that IFN β-1a 30 µg IM once a week was also less effective than IFN β-1a 44 µg SC three times a week in reducing steroid-treated relapses. Across disability progression outcomes, findings did not show a clear pattern, and the largest trial, EVIDENCE 2007,[191] did not find a significant difference on disability progression outcomes. Findings on MS symptoms and health-related quality of life were poorly reported and inconsistent, and relied on one small trial. We were unable to locate any comparisons on combined clinical-MRI measures of freedom from disease activity, and included studies did not report mortality.

9.5.3 IFN β-1a 30 µg IM once a week (Avonex) vs. IFN β-1b 250 µg SC every other day (Betaferon/Extavia)

Three trials compared IFN β-1a 30 µg IM once a week against IFN β-1b 250 µg SC every other day: Etemadifar 2006,[183] INCOMIN 2002[194] and Mokhber 2014.[184, 185]

Relapse outcomes

Findings for relapse outcomes relied on two trials, both with 24 months of follow-up. In Etemadifar 2006,[183] patients receiving IFN β-1a 30 µg IM once a week had fewer relapses over two years of follow-up than patients receiving IFN β-1b 250 µg SC every other day (57 vs. 65; n=30 in both groups). We estimated this as a rate ratio of 0.88 (95% CI [0.61, 1.25]). However, in INCOMIN 2002,[194] which followed up 188 patients over 24 months, patients receiving IFN β-1a 30 µg IM once a week had a higher ARR (0.7) than patients receiving IFN β-1b 250 µg SC every other day (0.5). Because authors presented the effect size estimate as a standardised mean difference, we re-estimated the rate ratio as 1.4 (95% CI [1.07, 1.83]).

Both trials suggested that the proportion of patients relapse free was comparatively higher in IFN β-1a 44 µg SC three times a week. Proportions of patients experiencing relapses were significantly different between the relevant arms in Etemadifar 2006,[183] with patients receiving IFN β-1a 30 µg IM once a week less likely to be free of relapse (20% vs. 43.3%, p=0.049). In INCOMIN 2002,[194] patients receiving IFN β-1a 30 µg IM once a week were also less likely to be free of relapse than patients receiving IFN β-1b 250 µg SC every other day (36% vs. 51%, risk ratio=0.76, 95% CI [0.59, 0.99]).

Relapse severity

Only INCOMIN 2002[194] presented findings for relapse severity; specifically, ARR for steroid-treated relapses. While patients receiving IFN β-1a 30 µg IM once a week were more likely to have steroid-treated relapses than those receiving IFN β-1b 250 µg SC every other day (0.5 vs. 0.38), this difference was not significant (estimated RR=1.32, 95% CI [0.96, 1.80]).

Disability progression

Only INCOMIN 2002[194] presented differences in time to disability progression confirmed at 6 months and for proportions with disability progression. More patients receiving IFN β-1a 30 µg IM once a week progressed as compared to patients receiving IFN β-1b 250 µg SC every other day (30% vs. 13%), with patients in the IFN β-1b 250 µg SC every other day group having a reduction in risk of progression of 56% (p=0.005). In combination with a log rank test reported as p<0.01, this gives an estimated hazard ratio of 2.24 (95% CI [1.21, 4.13]).

Findings from all three trials suggested that IFN β-1a 30 µg IM once a week did not have as beneficial an effect on magnitude of EDSS change as IFN β-1a 250 µg SC every other day. In Etemadifar 2006,[183] patients receiving IFN β-1a 30 µg IM once a week reduced EDSS score by 0.1 (95% CI [-0.2, 0.5]), a numerically smaller decrease than patients receiving IFN β-1a 250 µg SC every other day (0.7, [0.5, 0.9]). Again, formal pairwise significance testing was not reported. Moreover, in a comparatively small trial, Mokhber 2014[184, 185] found no evidence for a significant difference between baseline and 12-month follow-up on EDSS score for IFN β-1a 30 µg IM once a week (0.0, n=20, p=0.548), though a test for change was significant for IFN β-1b 250 µg SC every other day (-0.6, n=19, p=0.028). Pairwise testing was not performed but an overall test was not significant. Finally, in an ANCOVA-adjusted estimate, INCOMIN 2002[194] found that patients receiving IFN β-

1a 30 µg IM once a week had a higher EDSS score at end of trial than patients receiving IFN β-1a 250 µg SC every other day (2.5 vs. 2.1, p=0.004).

MS symptoms and health-related quality of life

Mokhber 2014[184] presented tests of cognitive function, though without pairwise comparisons. It should be reiterated that this was a small trial with 39 patients analysed in total in the relevant contrasts. On all tests presented (selective reminding test, spatial recall test, symbol digit modalities test, PASAT and word list generation), comparisons across all three treatment groups were not statistically significant except for the symbol digit modalities test. Post hoc tests found evidence that patients receiving IFN β-1a 30 µg IM once a week did not improve as much as patients receiving IFN β-1b 250 µg SC every other day on the symbol digit modalities and PASAT-easy tests.

Additionally, Mokhber 2014[185] disaggregated the MS Quality of Life-54 scale into its subcomponents, including mental health (five components) and physical health (eight components). There were few significant within-groups differences in this small trial, and pairwise significance tests, as well as estimates of change from baseline, were not presented in a standard format, permitting only discussion of direction and significance of differences. Patients receiving IFN β-1a 30 µg IM once a week significantly improved in health perceptions and pain as compared to patients receiving IFN β-1b 250 µg SC every other day, who declined on both measures. However, patients receiving IFN β-1b 250 µg SC every other day improved more on overall quality of life, overall mental health aspects of quality of life and emotional wellbeing as compared to patients receiving IFN β-1a 44 µg SC three times a week. Differences were not significant for overall physical health aspects of quality of life, physical function, energy/fatigue, physical role limitations, sexual function, social function, health distress, emotional role limitations or cognitive function.

Adverse events and mortality

Only INCOMIN 2002[194] reported adverse events. No studies reported mortality. Full results are available on request.

Summary of the narrative synthesis: IFN β-1a 30 µg IM once a week (Avonex) vs. IFN β-1b 250 µg SC every other day (Betaferon/Extavia)

Though trials were in conflict on the relative effect of the drugs on relapse rate, INCOMIN 2002[194] suggested that IFN β-1a 30 µg IM once a week was less effective than IFN β-1b 250 µg SC every other day in reducing relapse rate, and both studies found that the proportion of patients free of relapses was lower in IFN β-1a 30 µg IM once a week. INCOMIN 2002 did not find a difference on relapse severity, measured as steroid-treated relapses, but both studies agreed that IFN β-1a 30 µg IM once a week was less effective than IFN β-1b 250 µg SC every other day on disability progression. Findings on MS symptoms and health-related quality of life relied on one small trial with inconsistent effects and poor reporting. No studies reported mortality.

9.5.4 IFN β-1a 30 µg IM once a week (Avonex) vs. GA 20 mg SC once daily (Copaxone)

Two trials compared IFN β-1a 30 µg IM once a week against GA 20 mg SC once daily: Calabrese 2012[186] and CombiRx 2013.[189]

Relapse outcomes

Findings for relapse outcomes relied on two trials with substantial follow-up; one trial (CombiRx 2013[189]) was considerably larger than the other. In Calabrese 2012,[186] patients receiving IFN β-1a 30 µg IM once a week (n=47), when compared to patients receiving GA 20 mg SC once daily (n=48), did not appear to have a numerically different ARR (0.5 [SD=0.6]) vs. 0.5 [SD=0.4]) after two-year follow-up. A formal significance test was not reported, but we re-estimated the rate ratio as 1.00 (95% CI [0.67, 1.50]). However, in the larger CombiRx 2013[189] trial with 36-month follow-up, patients receiving IFN β-1a 30 µg IM once a week (n=250) had a higher ARR than patients receiving GA 20 mg SC once daily (0.16 vs. 0.11). This difference was tested using a Cox proportional hazards model with correction for repeated events, which found statistically significant evidence of a shorter time between relapses as compared to GA 20 mg SC once daily (HR=1.43, 95% CI [1.04, 1.95]). This finding was robust to a sensitivity analysis including non-protocol defined relapses.

However, CombiRx 2013[189] did not find a significant difference in time to first relapse between groups (p=0.19). Additional information was not reported. CombiRx 2013 also did not find a significant difference between groups in proportions with protocol defined relapses at 36 months (74.0% vs. 79.5%, p=0.14).

Relapse severity

We were unable to locate any relevant comparisons between IFN β-1a 30 µg IM once a week and GA 20 mg SC once daily on outcomes relating to moderate or severe relapses or steroid-treated relapses.

Disability progression

CombiRx 2013[189] reported proportions of patients with EDSS progression at 6 months. Fewer patients receiving IFN β-1a 30 µg IM once a week progressed as compared to patients receiving GA 20 mg SC once daily (21.6% vs. 24.8%) but this difference was reported as not statistically significant.

In Calabrese 2012,[186] patients receiving IFN β-1a 30 µg IM once a week had a numerically lower increase in EDSS scores at two years (0.2, SD=0.4) as compared to patients receiving GA 20 mg SC once daily (0.3, SD=0.5) but formal significance testing was not reported.

Freedom from disease activity

Only CombiRx 2013[189] reported freedom from disease activity outcomes in this comparison. In CombiRx 2013, proportions with freedom from disease activity (defined as absence of exacerbation, EDSS progression or combined unique lesion activity—i.e. no new of enhanced lesions, unenhanced T2 lesions or enlarged unenhanced T2 lesions) was not different (p=0.62) between patients receiving IFN β-1a 30 µg IM once a week

(21.2%) and patients receiving GA 20 mg SC once daily (19.4%). This finding was robust to the inclusion of non-protocol defined exacerbations (17.1% vs. 16.1%, *p*=0.762).

MS symptoms and health-related quality of life

In CombiRx 2013,[189] change from baseline to 36 months was measured for the Multiple Sclerosis Functional Composite and several of its components, but no differences between groups were significantly different. Overall MSFC improved slightly in both IFN β-1a 30 µg IM once a week (mean 0.1, SD=0.5) and in GA 20 mg SC once daily (mean 0.2, SD=0.5). Time in seconds complete the timed 25-foot walk increased slightly in both groups (0.2 [1.1] vs. 0.2 [1.7]) but time in seconds to complete the nine-hole peg test decreased slightly (-0.4 [3.8] vs. -0.1 [4.1]), and both groups improved in the number of questions correct in the PASAT (3.5 [8.1] vs. 4.3 [7.4]).

Adverse events and mortality

Only CombiRx 2013[189] reported AEs or mortality. Full results are available on request. One death occurred in each of the relevant arms of CombiRx 2013, and thus differences were not significant.

Summary of the narrative synthesis: IFN β-1a 30 µg IM once a week (Avonex) vs. GA 20 mg SC once daily (Copaxone)

Findings from two studies were mixed on relapse outcomes, but the larger of the two trials suggested that IFN β-1a 30 µg IM once a week was less effective than GA 20 mg SC once daily at reducing relapses. Findings for disability progression, combined clinical-MRI measures on freedom from disease activity or MS symptoms did not suggest a difference between the two drugs. We were unable to locate any evidence on relapse severity, defined as moderate or severe relapses or steroid-treated relapses. Mortality was rare and not different between drugs in CombiRx 2013.[189]

9.5.5 IFN β-1a 44 µg and 22 µg SC three times a week (Rebif) vs. placebo

Our analysis was informed by three trials comparing IFN β-1a 44 µg SC three times a week against no treatment: IMPROVE 2012,[205] PRISMS 1998[187] and REMAIN 2012.[181] REMAIN 2012[181] used best supportive care alone as a comparator, whereas the other two trials used placebo. As noted above, REMAIN 2012 is of limited interest but is included here for completeness. One trial, PRISMS 1998,[187] also compared IFN β-1a 22 µg SC three times a week against no treatment.

An additional six trials compared IFN β-1a 44 µg SC three times a week against other drugs: three multi-arm trials (Calabrese 2012,[186] Etemadifar 2006[183] and Mokhber 2014[184, 185]) and three two-arm trials (EVIDENCE 2007,[191-193] REFORMS 2012[195] and REGARD 2008[190]). Comparisons in EVIDENCE 2007[191-193] were discussed in the prior section.

Relapse outcomes

Both key studies reported relapse outcomes. PRISMS 1998,[187] which tested both doses of IFN β-1a SC three times a week, followed up 560 patients (n=184 in the 44 µg arm, n=189 in the 22 µg arm, n=187 in the placebo

arm) over two years. Relative to placebo, both the 44 µg dose (RR=0.73, 95% CI [0.61, 0.86]) and the 22 µg dose (0.67, [0.56, 0.79]) reduced the rate of relapses. IMPROVE 2012,[205] a comparatively short trial which followed up 180 patients over 16 weeks (n=120 in the 44 µg arm, n=60 in the placebo arm), showed a substantial decrease in rate of relapses for those receiving the study drug as well (0.43, [0.23, 0.82]). Time to first relapse outcomes were cursorily presented by PRISMS 1998.[187] Both the 44 µg and 22 µg doses delayed time to first relapse by 5 months and 3 months respectively, though a significance test was not presented. However, [redacted].

Finally, PRISMS 1998[187] reported proportions free of relapse. In both doses, proportions relapse-free were greater than placebo at two years of follow-up. As compared to a placebo arm with 16% free of relapses, patients receiving 44 µg had a 32% chance of being free of relapses (OR=2.57, 95% CI [1.56, 4.25]) and patients receiving 22 µg had a 27% chance of being free of relapses (2.01, [1.21, 3.35]).

REMAIN 2012,[181] which followed up 30 patients with either RRMS or SPMS for 96 weeks, did not find a significant difference between arms on time to first relapse or proportion relapse-free.

Relapse severity

PRISMS 1998[187] presented data for both moderate or severe relapses and steroid-treated relapses. Patients receiving placebo had, on average, more moderate or severe relapses over the course of the study (0.99) than patients receiving 44 µg of the study drug (0.62) or patients receiving 22 µg (0.71). We re-estimated these as rate ratios of 0.64 (95% CI [0.53, 0.74]) and 0.72 (0.61, 0.84) respectively. Correspondingly, patients receiving 44 µg were more likely to be free of any moderate or severe relapses (OR=2.32, 95% CI [1.47, 3.37]). Findings were similar for the 22 µg dose as compared to placebo (2.13, [1.41, 3.21]).

The pattern of findings in PRISMS 1998[187] for steroid treatments was similar. Patients receiving placebo had, on average, more courses of steroids for MS relapses over the course of the study (1.39) than patients receiving 44 µg (0.75) or patients receiving 22 µg (0.97). We re-estimated the corresponding rate ratios for 44 µg compared to placebo as 0.54 (95% CI [0.46, 0.63]) and for 22 µg compared to placebo as 0.70 (0.61, 0.80]). Correspondingly, patients receiving 44 µg were more likely to be free of any steroid-treated relapses (OR=1.99, 95% CI [1.32, 3.02]), as were patients receiving 22 µg (1.71, [1.14, 2.57]).

Disability progression

In PRISMS 1998,[187] time to disability progression confirmed at 3 months was slowed by both doses of the study drug as compared to placebo. The 25th percentile of the distribution of time to progression was 21.3 months for patients receiving 44 µg and 18.5 months for patients receiving 22 µg, as compared to 11.9 for patients receiving placebo. Corresponding hazard ratios showed evidence of statistically significant delay of progression (44 µg: HR=0.62, 95% CI [0.43, 0.91]; 22 µg: 0.68, [0.48, 0.98]).

Both PRISMS 1998[187] and IMPROVE 2012[205] reported the magnitude of EDSS change. As compared to placebo in PRISMS 1998,[187] both 44 µg and 22 µg had a smaller increase in EDSS score. The difference was 0.25 EDSS points (both $p<0.05$). IMPROVE 2012[205] did not report a standard significance test, though median EDSS changes in both the 44 µg and the placebo arm were 0.

In REMAIN 2012,[181] magnitude of EDSS change, time to progression and proportions with progressing were not significantly different between arms.

Freedom from disease activity

We were unable to locate any relevant comparisons between IFN β-1a 44 µg or 22 µg SC three times a week and placebo on combined clinical-MRI outcomes for freedom from disease activity.

MS symptoms and health-related quality of life

PRISMS 1998 reported effects of IFN β-1a 44 µg and 22 µg SC three times a week on various MS symptoms across two publications.[187, 206] As noted in the original trial report,[187] patients receiving the 44 µg dose were less likely to have a sustained worsening in ambulation as compared to placebo (7% vs. 13%, $p<0.05$), but the proportion in patients receiving the 22 µg dose (12%) was not significantly different from placebo. Subsequently, Gold and colleagues[206] reported that though patients in all three groups increased from baseline on the Center for Epidemiological Studies Depression Rating Scale, these changes were not different between groups (44 µg: 0.2, 22 µg: 1.8, placebo: 0.9; $p=0.60$). Similarly, risk of exceeding the cutoff score for depression on this scale was not different in 44 µg (risk ratio=0.7, 95% CI [0.3, 1.6]) or 22 µg (0.8, [0.3, 1.8]) as compared to placebo, and proportions of patients exceeding the cutoff on the Beck Hopelessness Scale were not different between placebo (6.9%) and either 44 µg (6.9%, $p=1.0$) or 22 µg (10.5%, $p=0.55$). Finally, data were not presented numerically, but groups were reported as having no difference in scores on the General Health Questionnaire, nor on its subscales.

Adverse events and mortality

All studies presented AEs. Full results are available on request. None of the studies reported deaths related to the study drugs.

Summary of the narrative synthesis: IFN β-1a 44 µg and 22 µg SC three times a week (Rebif) vs. placebo

Findings from two trials suggested a beneficial effect of IFN β-1a 44 µg SC three times a week against placebo on relapse outcomes. Additionally, findings from PRISMS 1998[187] suggested a beneficial effect of IFN β-1a 44 µg SC three times a week on relapse severity (both moderate/severe relapses and steroid-treated relapses) and on delaying disability progression. Findings from PRISMS 1998[187, 206] also suggested a beneficial effect of the IFN

β-1a 44 µg SC three times a week on ambulation, but not mental health. Findings for the 22 µg dose in PRISMS 1998[187, 206] were similar except for ambulation. Mortality was not reported.

9.5.6 IFN β-1a 44 µg SC three times a week (Rebif) vs. IFN β-1b 250 µg SC every other day (Betaferon/Extavia)

Three trials compared IFN β-1a 44 µg SC three times a week against IFN β-1b 250 µg SC every other day: Etemadifar 2006,[183] Mokhber 2014[184, 185] and REFORMS 2012.[195] An additional trial, AVANTAGE 2014,[180] compared these drugs on adverse events.

Relapse outcomes

Assessment of relapse outcomes in this comparison relied on two small studies with very different follow-up. In Etemadifar 2006,[183] patients receiving IFN β-1a 44 µg SC three times a week had 66 relapses, as compared to 65 relapses in patients receiving IFN β-1b 250 µg SC every other day, all over two years of follow-up (n=30 in both groups). We estimated this as a rate ratio of 1.02 (95% CI [0.72, 1.43]). In REFORMS 2012,[195] patients receiving IFN β-1a 44 µg SC three times a week had an ARR of 0.15 as compared to patients receiving IFN β-1b 250 µg SC every other day, who had an ARR of 0.11. This difference was statistically significant (p<0.001), though this was a relatively small trial (n=129), patients were only followed up for 12 weeks and patient relapses were self-reported rather than assessed by a neurologist.

In Etemadifar 2006,[183] the proportion of patients without relapses at two years was numerically higher in IFN β-1a 44 µg SC three times a week against IFN β-1b 250 µg SC every other day (56.7% vs. 43.3%), but no pairwise significance testing was performed.

Relapse severity

We were unable to find any comparisons between IFN β-1a 44 µg SC three times a week and IFN β-1b 250 µg SC every other day on outcomes relating to moderate or severe relapses or steroid-treated relapses.

Disability progression

Analysis of disability progression in both trials was by magnitude of EDSS change, though both trials inadequately reported analysis details. In Etemadifar 2006,[183] patients receiving IFN β-1a 44 µg SC three times a week had a decrease in EDSS score of 0.3 (95% CI [0.03, 0.5]), as compared to a decrease of 0.7 (0.5, 0.9) in patients receiving IFN β-1b 250 µg SC every other day. A pairwise significance test was not performed. Patients in Mokhber 2014[184, 185] also decreased in EDSS score across both comparisons, but in the opposite direction (-1.0, p=0.001 vs. -0.6, p=0.028). Again, a pairwise significance test was not performed.

Freedom from disease activity

We were unable to find any comparisons between IFN β-1a 44 µg SC three times a week and IFN β-1b 250 µg SC every other day on outcomes relating to combined clinical-MRI outcomes for freedom from disease activity.

MS symptoms and health-related quality of life

As noted previously, analyses in Mokhber 2014[184] for cognitive function were not significant across groups but for the symbol digit modalities test. Post hoc analyses indicated that patients receiving IFN β-1a 44 µg SC three times a week improved more than IFN β-1b 250 µg SC every other day on tests of the symbol digit modalities test and the PASAT-easy.

Across the quality of life domains tested in Mokhber 2014[185], IFN β-1a 44 µg SC three times a week was not significantly different from IFN β-1b 250 µg SC every other day but for overall mental health aspects of health-related quality of life, where patients receiving IFN β-1b 250 µg SC every other day improved significantly more.

Adverse events and mortality

AEs were only reported by AVANTAGE 2014[180] and REFORMS 2012.[195] Only AVANTAGE 2014 reported death, but no events occurred in either study arm. Full results are available on request.

Summary of the narrative synthesis: IFN β-1a 44 µg SC three times a week (Rebif) vs. IFN β-1b 250 µg SC every other day (Betaferon/Extavia)

Findings were derived from three small trials and should thus be treated with caution. Two trials reporting relapse outcomes disagreed, though there was some evidence from REFORMS 2012[195] that patients receiving IFN β-1a 44 µg SC three times a week had a higher ARR. Findings for disability progression, MS symptoms and health-related quality of life were inconsistent and poorly reported. We were unable to find comparisons for relapse severity or combined clinical-MRI measures of freedom from disease activity. No deaths were reported.

9.5.7 IFN β-1a 44 µg SC three times a week (Rebif) vs. GA 20 mg SC once daily (Copaxone)

Two trials compared IFN β-1a 44 µg SC three times a week against GA 20 mg SC once daily: Calabrese 2012[186] and REGARD 2008.[190]

Relapse outcomes

In Calabrese 2012,[186] patients receiving IFN β-1a 44 µg SC three times a week had a numerically lower ARR than patients receiving GA 20 mg SC once daily after two years of follow up (0.4 [SD=0.6] vs. 0.5 [SD=0.4]), but formal significance testing was not reported and relapses were analysed using a normal distribution. We re-estimated this rate ratio as 0.80 (95% CI [0.52, 1.23]). In the larger REGARD 2008[190] trial, 764 patients were followed up for 96 weeks. ARRs were not significantly different between patients receiving IFN β-1a 44 µg SC three times a week and patients receiving GA 20 mg SC once daily (0.30 vs. 0.29, p=0.828).

REGARD 2008[190] did not find a significant difference in time to first relapse between patients receiving IFN β-1a 44 µg SC three times a week and those receiving GA 20 mg SC once daily (HR=0.94, 95% CI [0.74, 1.21]), nor did the trial find a difference in patients free of relapses at 96 weeks (62% vs. 62%, p=0.96).

Relapse severity

In REGARD 2008,[190] the ARR for steroid-treated relapses was not significantly different between patients receiving IFN β-1a 44 µg SC three times a week and those receiving GA 20 mg SC once daily (0.19 vs. 0.17, *p*=0.386).

Disability progression

REGARD 2008[190] reported proportions of patients with disability progression confirmed at 6 months. Proportions were not significantly different (*p*=0.117) between patients receiving IFN β-1a 44 µg SC three times a week (11.7%) and those receiving GA 20 mg SC once daily (8.7%).

In Calabrese 2012,[186] patients receiving IFN β-1a 44 µg SC three times a week had a numerically lower increase in EDSS scores at two years (0.2, SD=0.5) as compared to patients receiving GA 20 mg SC once daily (0.3, SD=0.5) but formal significance testing was not reported.

Freedom from disease activity

We were unable to locate any comparisons between IFN β-1a 44 µg SC three times a week and GA 20 mg SC once daily on combined clinical-MRI outcomes for freedom from disease activity.

MS symptoms and health-related quality of life

We were unable to locate any comparisons between IFN β-1a 44 µg SC three times a week and GA 20 mg SC once daily on MS symptoms or health-related quality of life.

Adverse events and mortality

AEs and mortality were reported by REGARD 2008.[190] Only one death occurred, in the IFN arm, and thus mortality was not significantly different between groups. Full results are available on request.

Summary of the narrative synthesis: IFN β-1a 44 µg SC three times a week (Rebif) vs. GA 20 mg SC once daily (Copaxone)

Findings from two trials did not suggest the presence of a difference between the two drugs on relapse outcomes, relapse severity or disability progression. We could not locate comparisons relating to combined clinical-MRI measures of freedom from disease activity or to MS symptoms or health-related quality of life. Mortality was not different between groups.

9.5.8 IFN β-1b 250 µg SC every other day (Betaferon/Extavia) vs. placebo

We included two trials comparing IFN β-1b 250 µg SC every other day against placebo: IFNB Multiple Sclerosis Study Group 1995 (referred to as IFNB MSSG 1995[207, 208]) and Knobler 1993.[209] Schwartz 1997[179] examined quality of life outcomes only, and used best supportive care instead of placebo.

An additional 6 trials compared IFN β-1b 250 µg SC every other day against other drugs: two multi-arm trials (Etemadifar 2006,[183] Mokhber 2014[184, 185]) and four two-arm trials (BECOME 2009,[182] BEYOND 2009,[188] INCOMIN 2002,[194] REFORMS 2012[195]). Comparisons for Etemadifar 2006,[183] Mokhber 2014[184, 185], INCOMIN 2002[194] and REFORMS 2012[195] have been discussed in previous sections.

Relapse outcomes

Both studies reporting ARRs suggested a beneficial effect of IFN β-1b 250 µg SC every other day, though only IFNB MSSG 1995[207, 208] may have been powered to detect a difference. In IFNB MSSG 1995,[207, 208] 247 patients in the relevant arms were followed up for variable amounts of time, with the initial two-year study phase continuing into a blinded extension; thus, some patients were followed for up to 5.5 years, with median follow up 46.0 months for the placebo arm and 48.0 months for the relevant study drug arm. At the end of the study, patients receiving IFN β-1b 250 µg SC every other day had a lower ARR than patients receiving placebo (0.78, 95% CI [0.70, 0.88] vs. 1.12, 95% CI [1.02, 1.23]; p=0.0006). In a comparatively small trial, Knobler 1993[209] followed up 30 patients over three years, including a six-month dose-finding period at the start of the study. The 24 patients receiving IFN β-1b 250 µg SC every other day had an ARR of 0.7 as compared to the 6 patients receiving placebo, who had an ARR of 0.9. This difference was not significant (p=0.33).

Both studies also reported information on time to first relapse. Knobler 1993[209] reported that median time to first relapse was delayed, but not significantly so, in patients receiving IFN β-1b 250 µg SC every other day as compared to patients receiving placebo (14 months vs. 2 months, log rank p=0.07). The comparatively larger IFNB MSSG 1995 reported a similar finding at the three-year follow-up,[207] albeit at smaller magnitude and rising to statistical significance. Median time to first exacerbation was delayed in patients receiving IFN β-1b 250 µg SC every other day as compared to placebo (264 days vs. 147 days, log rank p=0.028).

Proportions free of relapse were also only available at the three-year follow-up for IFNB MSSG 1995.[207] Proportions free of relapse were not significantly different between groups (IFN β-1b 250 µg SC every other day 21.8% vs. placebo 13.8%, p=0.097). Three-year results from Knobler 1993[209] showed a similar trend (42% vs. 17%), though these findings were not significant either (p=0.37).

Relapse severity

Relapse severity was reported based on both two-year and final data from IFNB MSSG 1995,[207, 208] but only results from the two-year data were usable. At two years of follow-up, patients receiving IFN β-1b 250 µg SC every other day had a lower ARR for moderate or severe relapses as compared to placebo (0.23 vs. 0.45, p=0.002). Similar findings based on final data reported only a p-value (p=0.012) for a relationship in the same direction. Knobler 1993[209] did not find a significant relationship for 'attack severity', though findings were only reported as a non-significant p-value (p=0.67) and relapse severity was not defined.

Disability progression

IFNB MSSG 1995 reported that IFN β-1b 250 µg SC every other day delayed disability progression confirmed at 3 months, but not significantly so, with median time to progression of 4.79 years as compared to 4.18 years in

placebo (log rank p=0.096).[208] Proportions with confirmed progression showed a similar trend (35% vs. 46%). We re-estimated this as a hazard ratio of 0.71 (95% CI [0.48, 1.06]). Knobler 1993[209] examined change from baseline EDSS between groups, but only noted that the difference was not statistically significant (p=0.42).

Freedom from disease activity

We were unable to locate any relevant comparisons between IFN β-1b 250 µg SC every other day and placebo for combined clinical-MRI outcomes relating to freedom from disease activity.

MS symptoms and health-related quality of life

In Schwartz 1997,[179] 34 patients receiving IFN β-1b 250 µg SC every other day were compared against 45 patients receiving best supportive care. Over the course of a year, patients were not different on quality-adjusted time without symptoms and toxicity, measured in months (106 vs. 10.4, p=0.50).

Adverse events and mortality

AEs were reported by IFNB MSSG 1995[208] and Knobler 1993.[209] None of the studies reported mortality. Full results are available on request.

Summary of the narrative synthesis: IFN β-1b 250 µg SC every other day (Betaferon/Extavia) vs. placebo

Findings from two studies suggested a beneficial effect of IFN β-1b 250 µg SC every other day on relapse outcomes as compared to placebo (though not for proportions relapse-free). Findings from IFNB MSSG 1995[207, 208] suggested a reduction in rate of moderate or severe relapses, but findings from Knobler 1993[209] were uninterpretable. Neither study found evidence of delaying time to disability progression. One small study comparing IFN β-1b 250 µg SC every other day against best supportive care did not find differences in health-related quality of life over a year. We were unable to find comparisons for combined clinical-MRI freedom from disease activity. None of the studies reported mortality.

9.5.9 IFN β-1b 250 µg SC every other day (Betaferon/Extavia) vs. GA 20 mg SC once daily (Copaxone)

Two trials compared IFN β-1b 250 µg SC every other day against GA 20 mg SC once daily: BECOME 2009[182] and BEYOND 2009.[188]

Relapse outcomes

Both BECOME 2009[182] and the larger BEYOND 2009[188] trial reported ARRs. In BECOME 2009,[182] 75 patients were followed up for up to two years. Patients receiving IFN β-1b 250 µg SC every other day did not have a significantly different ARR than patients receiving GA 20 mg SC once daily (0.37 vs. 0.33, p=0.68).

Findings from BEYOND 2009,[188] in which 1345 patients from the relevant trial arms were followed up for at least two and up to 3.5 years, suggested a similar trend (0.36 vs. 0.34, one-tailed p=0.79). This was expressed using a Cox proportional hazards model with modification for repeated events (HR=1.06, 95% CI [0.89, 1.26]).

Time to first relapse was also not significantly different between arms in either study. In BECOME 2009,[182] of patients who had relapses, median time for those receiving IFN β-1b 250 µg SC every other day (123 days) was not very different from those receiving GA 20 mg SC once daily (121 days), with a non-significant log rank test on the whole sample (p=0.12). In BEYOND 2009,[188] patients at the 25th percentile did not have substantially different days to first relapse (IFN β-1b 250 µg SC every other day 283 vs. GA 20 mg SC once daily 271; one-sided log rank p=0.75). This was supported by proportions relapse-free at two years estimated from a Kaplan-Meier model, which were very similar (59% vs. 58%).

Finally, only BECOME 2009[182] reported empirical proportions of patients relapsing. Fewer patients receiving IFN β-1b 250 µg SC every other day were relapse free as compared to patients receiving GA 20 mg SC once daily, but this difference was not significant (53% vs. 72%, p=0.10).

Relapse severity

Only BEYOND 2009[188] reported ARRs for severity of relapse. ARRs for major relapse were not significantly different between patients receiving IFN β-1b 250 µg SC every other day and those receiving GA 20 mg SC once daily (0.19 vs. 0.18, one-sided p=0.36). Time to first major relapse was not significantly different, with both arms having proportions at two years of 27%as predicted by a Kaplan-Meier model (log rank p=0.56).

Both studies reported empirical proportions for patients receiving steroid treatment for MS. In BECOME 2009,[182] more patients receiving IFN β-1b 250 µg SC every other day (44%) required steroid treatment for relapses than patients receiving GA 20 mg SC once daily (23%), but this difference was only of marginal significance (p=0.09). In contrast, proportions of patients requiring steroid treatment for relapses were not meaningfully different in BEYOND 2009[188] (34% vs. 32%, p=0.43).

Disability progression

BEYOND 2009[188] reported time to disability progression confirmed at 3 months. Because median time to progression was not reached, the time to progression at the 10th percentile was reported. The 10th percentile of patients receiving IFN β-1b 250 µg SC every other day progressed after 274 days, whereas patients receiving GA 20 mg SC once daily progressed after 268 days (log rank p=0.35). Alternative estimates were provided based on Kaplan-Meier models, in which the probability of progression at the end of two years was 21% in those receiving IFN β-1b 250 µg SC every other day and 20% in those receiving GA 20 mg SC once daily (log rank p=0.68). We estimated a hazard ratio of 1.06 (95% CI [0.81, 1.37]) from these statistics.

In a separate publication to the main trial report, BECOME 2009[210] reported time to disability progression confirmed at 6 months. Empirical proportions of patients progressing in each arm were dissimilar (IFN β-1b 250 µg SC every other day 12.1% vs. GA 20 mg SC once daily 17.6%), but with a non-significant log rank test

(p=0.51). Based on these statistics, we estimated a hazard ratio of 0.66 (95% CI [0.19, 2.28]). BECOME 2009[210] also reported progression based on the MS Functional Composite, in which an increase of 0.2 SD confirmed at 6 months constitutes evidence of progression. The same trend was apparent (5.7% vs. 10.3%, log rank p=0.39).

Freedom from disease activity

We were unable to locate any relevant comparisons between IFN β-1b 250 µg SC every other day and GA 20 mg SC once daily on combined clinical-MRI measures of freedom from disease activity.

MS symptoms and health-related quality of life

We were unable to locate any relevant comparisons between IFN β-1b 250 µg SC every other day and GA 20 mg SC once daily on MS symptoms or health-related quality of life. However, BECOME 2009[182] did present results for the MS Functional Composite, discussed above.

Adverse events and mortality

Both studies reported AEs, but only BEYOND 2009[188] reported mortality. Differences were not significant for mortality, though only one death occurred, in the GA arm of BEYOND 2009. Full results are available on request.

Summary of the narrative synthesis: IFN β-1b 250 µg SC every other day (Betaferon/Extavia) vs. GA 20 mg SC once daily (Copaxone)

Findings from two trials—one small and one large—did not suggest a difference between the two drugs on relapse outcomes, relapse severity, or disability progression. We were unable to locate any comparisons for combined clinical-MRI measures on freedom from disease activity. Differences between groups were not significant for mortality.

9.5.10 Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy) vs. placebo

We included one trial comparing pegylated IFN β-1a 125 µg SC every two weeks against placebo: ADVANCE 2014.[211] We were unable to locate any trials including comparisons between pegylated IFN β-1a 125 µg SC every two weeks and other drugs. In its placebo-controlled phase, ADVANCE 2014 compared pegylated IFN β-1a 125 µg SC every two weeks and every four weeks against placebo for 48 weeks. The relevant arms included a total of 1012 patients analysed.

Relapse outcomes

Participants receiving pegylated IFN β-1a 125 µg SC every two weeks had a decrease in ARR (RR=0.644, 95% CI [0.500-0.831]).[211] Time to first relapse was also delayed in patients receiving the active drug (HR=0.61, 95% CI [0.47, 0.80]).

Relapse severity

Publications arising from this study did not report relapse severity.

Disability progression

Participants receiving pegylated IFN β-1a 125 µg SC every two weeks experienced a delay in time to disability progression confirmed at three months (HR=0.62, 95% CI [0.40, 0.97]).[211] As reported in the summary of product characteristics filed by the European Medicines Agency, the time to disability progression confirmed at six months was longer in patients receiving the study drug than in patients receiving placebo (0.46, [0.26, 0.81]).

Freedom from disease activity

In ADVANCE 2014, measures of freedom from disease activity included mixed clinical and MRI, clinical only, and MRI only definitions, and were reported in a publication separate to the main study report.[212] As stated in the methods, we report here the mixed clinical and MRI definition, which included both absence of relapses and of onset of disability progression confirmed at three months as well as no gadolinium-enhancing lesions and no new or newly enlarging T2 hyperintense lesions. Between baseline and week 48 of the trial, 33.9% of patients (n=466 in this analysis) receiving the study drug had no evidence of disease activity, whereas 15.1% of patients (n=484 in this analysis) receiving placebo did (OR=2.89, 95% CI [2.11, 3.95]). This finding was robust to sensitivity analysis on data missingness.

MS symptoms and health-related quality of life

In ADVANCE 2014, patients receiving pegylated IFN β-1a 125 µg SC every two weeks did not significantly worsen over 48 weeks on the MSIS-29 physical subscale (MD=0.08, 95% CI [-1.10, 1.27]) although placebo patients did (1.24, [0.05, 2.44]).[213] Both groups improved on the MSIS-29 psychological subscale, though differences were not significant between groups (pegylated IFN β-1a: -2.06 [-3.58, -0.53]; placebo: -2.17, [-3.63, -0.70]). Participants also completed the SF-12 (both the Physical Component Summary and the Mental Component Summary), EQ-5D, and EQ-5D visual analogue scale. None of the differences between groups or within groups were statistically significant (authors did not present specific data) but patients receiving pegylated IFN β-1a every two weeks did have a significant improvement on the visual analogue scale (2.06, [0.58, 3.54]).

Adverse events and mortality

ADVANCE 2014[211] reported AEs and mortality. Full results are available on request. Differences between groups for mortality were not significant, but one event occurred in the study drug arm and two events occurred in the placebo arm.

Summary of the narrative synthesis: pegylated IFN β-1a 125 µg SC every two weeks (Plegridy) vs. placebo

Findings from the one study included in this comparison suggested a beneficial effect of pegylated IFN β-1a 125 µg SC every two weeks against placebo on relapse outcomes, disability progression, and freedom from disease activity. Pegylated IFN β-1a 125 µg SC every two weeks were not different from placebo on health-related quality of life measures. Relapse severity outcomes were not reported. Groups were not significantly different on mortality.

9.5.11 GA 20 mg SC once daily and 40 mg SC three times a week (Copaxone) vs. placebo

We included five trials comparing GA 20 mg SC once daily against placebo: Bornstein 1987,[168] CONFIRM 2012,[214] Copolymer 1 Multiple Sclerosis Study Group 1995 (referred to as Cop1 MSSG 1995[215, 216]), European/Canadian Glatiramer Acetate Study Group 2001 (referred to as ECGASC 2001[217]), and GATE 2015.[218] One trial, GALA 2013,[219] tested GA 40 mg SC three times a week against placebo.

Additionally, one multi-arm trial (Calabrese 2012[186]) and four two-arm trials (BECOME 2009,[182] BEYOND 2009,[188] CombiRx 2013[189] and REGARD 2008[190]) compared GA 20 mg SC once daily against other drugs. These comparisons have been discussed above in the relevant sections.

Relapse outcomes

All five studies comparing GA 20 mg SC once daily against placebo reported relapse rate, as did the one study comparing GA 40 mg SC three times a week against placebo. Bornstein 1987[168] followed up 48 patients over two years. With a total of 16 relapses over two years in the 25 patients receiving GA 20 mg SC once daily and 62 relapses in the 23 patients receiving placebo, we estimated this as a rate ratio of 0.25 (95% CI [0.14, 0.43]). In another early study, Cop1 MSSG 1995[215, 216] followed up 251 patients over at least two years, with an extension of up to 11 months. At two years, the ARR in patients receiving GA 20 mg SC once daily was 0.59, as compared to patients receiving placebo, who had an ARR of 0.84.[215] This difference was statistically significant (p=0.007). Subsequent studies found similar reductions in ARR. In ECASG 2001,[217] which followed up 239 patients over nine months, ARR in the study drug group was 0.81 as compared to 1.21 in placebo (RR=0.67, p=0.012). CONFIRM 2012[214] followed up 713 patients in relevant study arms for two years and found a significant difference in ARRs as well (GA 20 mg SC once daily 0.29 vs. placebo 0.40, RR=0.71, 95% CI [0.55, 0.93]). However, in a trial following up 357 patients receiving branded GA against 84 patients receiving placebo for nine months (GATE 2015),[218] ARRs were not substantially different between groups (GA 20 mg SC once daily 0.40, 95% CI [0.26, 0.62] vs. placebo 0.38, 95% CI [0.22, 0.66]), though a standard significance test was not presented. GALA 2013[219] compared GA 40 mg three times a week against placebo in 1404 patients (n=943 GA 40 mg three times a week vs. n=461 placebo) over 12 months. Patients receiving the study drug had a significantly lower ARR than patients receiving placebo (GA 40 mg SC three times a week 0.33, 95% CI [0.28, 0.39] vs. placebo 0.51, 95% CI [0.42, 0.61]) with an associated significant rate ratio (0.66, 95% CI [0.54, 0.80]).

Two studies reported time to relapse. Including the extension phase, patients receiving GA 20 mg SC once daily in Cop1 MSSG 1995[216] had a delayed time to first relapse as compared to patients receiving placebo, but this difference was not significant (median days to first relapse 287 vs. 198, p=0.057). However, in the larger CONFIRM 2012[214] trial, patients receiving GA 20 mg SC once daily did have a significant delay in time to relapse (HR=0.71, 95% CI [0.55, 0.92]). Patients receiving GA 40 mg three times a week in GALA 2013[219] also had longer median time to first relapse (393 days vs. 377 days), with a hazard ratio of 0.61 (95% CI [0.49, 0.74]).

Finally, empirical proportions free of relapse tended to be greater in patients receiving GA 20 mg SC once daily as compared to patients receiving placebo, but this trend was not completely consistent. In Bornstein 1987,[168] 56% of patients receiving the study drug were relapse-free at two years as opposed to 26% of patients receiving placebo (adjusted OR=4.6, p=0.036). Similarly, Cop1 MSSG 1995[216] found that over the whole trial, patients receiving the study drug were more likely to be free of relapses (33.6% vs. 24.6%, p=0.002). In ECGASC 2001,[217] this trend did not rise to significance (55.5% vs. 49.2%, OR=1.47, 95% CI [0.84, 2.56]), and in GATE 2015,[218] proportions were not substantially different (73.9% vs. 73.8%), though a significance test was not provided. In GALA 2013,[219] patients receiving GA 40 mg three times a week were more likely to be free of relapses than patients receiving placebo (77.0% vs. 65.5%, OR=1.93, 95% CI [1.49, 2.49]).

Relapse severity

In ECGASC 2001,[217] patients receiving GA 20 mg SC once daily had fewer steroid treated relapses (54 vs. 84). We estimated this as a rate ratio for steroid-treated relapses of 0.65 (95% CI [0.46, 0.91]). The proportion of patients with steroid-treated relapses was correspondingly lower (33.6% vs. 39.2%) but this was not tested for significance. In GALA 2013,[219] patients receiving GA 40 mg SC three times weekly had a lower ARR (0.30, 95% CI [0.25, 0.36]) for 'severe' relapses, defined as steroid-treated or hospitalised relapses, than patients receiving placebo (0.47, [0.38, 0.57]). This translated into a rate ratio of 0.64 (95% CI [0.53, 0.79]).

Disability progression

Three studies presented data on time to disability progression confirmed at 3 months, whereas only CONFIRM 2012[214] presented data time to progression confirmed at 6 months. Studies suggested a beneficial, but generally not significant, impact of GA 20 mg SC once daily on confirmed disability progression. In Bornstein 1987,[168] the median time to progression confirmed at 3 months was not reached for patients receiving GA 20 mg SC once daily, but was 18 months for patients receiving placebo. This difference was significant (log rank p=0.05). Together with proportions of patients with progression of 20% in the study drug arm and 48% in the placebo arm, we estimated the hazard ratio of progression as 0.37 (95% CI [0.14, 1.00]). In Cop1 MSSG 1995,[216] probabilities of non-progression were 76.8% in the GA 20 mg SC once daily arm as compared to 70.6% in the placebo arm. Using the value from a related significance test (p=0.199), we estimated the hazard ratio as 0.76 (95% CI [0.50, 1.16]). Finally, CONFIRM 2012[214] did not find that GA 20 mg SC once daily slowed time to progression confirmed at 3 months (HR=0.93, 95% CI [0.63, 1.37]). This finding was not different when disability progression was confirmed at 6 months (0.87, [0.55, 1.38]).

Only two studies presented data on proportions of patients with confirmed disability progression in comparisons of GA 20 mg SC once daily against placebo. As noted above, in Bornstein 1987,[168] 20% of patients receiving GA 20 mg SC once daily progressed over two years, while 48% of patients receiving placebo progressed. In univariate analyses, this finding was not significant (p=0.064), but multivariate analyses found a significant effect on probability of progression (p=0.033). In Cop1 MSSG 1995,[216] proportions with progression confirmed at 3 months were 23.2% in patients receiving GA 20 mg SC once daily as opposed to 29.4% in patients receiving placebo over the whole trial. In GALA 2013,[219] which compared GA 40 mg SC three times weekly against placebo, 95.5% of patients receiving the study drug were free of confirmed progression as compared to 96.3% of patients receiving placebo, but a formal significance test was not presented.

Finally, magnitude of EDSS change was reported by most studies, but changes were small across studies. In Bornstein 1987,[168] findings were presented as proportions improving or worsening by magnitude of improvement. We estimated that patients receiving GA 20 mg SC once daily improved by 0.12 EDSS points and patients receiving placebo worsened by 0.74 EDSS points, with a significant difference between groups (p<0.05). In Cop1 MSSG 1995,[216] patients receiving GA 20 mg SC once daily did not have a significant improvement in EDSS score (-0.11, 95% CI [-0.31, 0.10]) while patients receiving placebo had significant worsening (0.34, [0.13, 0.54]). This difference was statistically significant (p=0.006). In ECGASC 2001,[217] mean EDSS change from baseline was not significantly different between groups (GA 20 mg SC once daily 0.02 vs. placebo 0.05) but a p-value or confidence intervals were not presented. In GATE 2015,[218] neither patients receiving the study drug (-0.08, [-0.19, 0.03]) nor patients receiving placebo (-0.02, [-0.17, 0.14]) had significant improvements in EDSS score. Change in GALA 2013[219] was negligible as well (GA 40 mg SC three times weekly 0.0, SD=0.6 vs. placebo 0.1, SD=0.6).

Freedom from disease activity

GATE 2015[218] was the only study that reported combined clinical-MRI findings for freedom from disease activity. Proportions were slightly greater in patients receiving GA 20 mg SC once daily (9.2% vs. 7.1%), with similar findings once proportions were adjusted for stratification variables (8.5% vs. 6.6%). A formal significance test was not presented.

MS symptoms and health-related quality of life

CONFIRM 2012[214] presented data for health-related quality of life disaggregated by subscale of the SF-36. Compared to placebo, which showed a negative trend, change from baseline in the GA 20 mg SC once daily group was positive and the two groups were significantly different on the physical component summary (p=0.0259). However, the groups were not significantly different on the mental component summary. GA 20 mg SC once daily significantly improved (p<0.05) over placebo in physical functioning (0.3 vs. -2.2), bodily pain (2.3 vs. -1.3), and general health (1.9 vs. -0.6), but not physical (0.3 vs. -2.2) or emotional (1.4 vs. -3.3) aspects of role limitation, vitality (1.1 vs. 0.4), social functioning (-0.6 vs. -0.1), or mental health (0.3 vs. 0.6). Changes in EQ-5D scores were not presented, but were stated to be stable in all groups over the course of the study. As compared to placebo, patients receiving GA 20 mg SC once daily were not more likely to have been

stable or improved in either the physical component (OR=1.24, 95% CI [0.83, 1.85]) or the mental component (1.22, [0.82, 1.83]) of the SF-36.

At two years in Cop1 MSSG 1995,[215] the mean ambulation index scores were not different between patients receiving GA 20 mg SC once daily (0.27) and patients receiving placebo (0.28).

Adverse events and mortality

We stratified comparisons by type of placebo. All studies reported AEs, but only GALA 2013,[219] GATE 2015[218] and CONFIRM 2012[214] reported deaths. Only one death occurred, in the placebo arm of GALA 2013,[219] in studies with matched placebos; in CONFIRM 2012,[214] one death occurred in each arm. Full results are available on request.

Summary of the narrative synthesis: GA 20 mg SC once daily and 40 mg SC three times a week (Copaxone) vs. placebo

Taken together, findings from the five trials testing GA 20 mg SC once daily and the one trial testing GA 40 mg SC three times a week suggested a beneficial effect on relapse outcomes. Both studies (GA 20 mg: EGCASG 2001;[217] GA 40 mg: GALA 2013[219]) reporting relapse severity outcomes also found an effect of the study drug on decreasing the rate of steroid-treated relapses. Findings for disability progression were less convincing, and studies generally did not present significant results. Only one study presented combined clinical-MRI measures of freedom from disease activity, and this study did not show a large difference between groups, though significance testing was not undertaken. One study showed some effects of GA 20 mg SC once daily on health-related quality of life measures. Groups were not significantly different on mortality.

9.5.12 Meta-analyses: relapse rate

Pairwise meta-analyses

Direct evidence from comparisons against placebo is shown in Figure 6. All drugs had a statistically significant beneficial effect on relapse rate as compared to placebo. Findings for IFN β-1a pegylated SC 125 μg every two weeks, for GA 40 mg SC thrice weekly and for IFN β-1a 22 μg SC thrice weekly all relied on one study. Comparisons that relied on multiple studies were diverse in heterogeneity. Heterogeneity ranged from I^2 of 0% (IFN β-1b 250 μg SC every other day, IFN β-1a 30 μg IM once a week) to I^2 of 43% (IFN β-1a 44 μg SC thrice weekly) and 73% (GA 20 mg SC once daily). However, there were too few studies in each comparison to enable exploration of heterogeneity.

Direct evidence from comparisons between active drugs is shown in Figure 7. None of the pooled comparisons showed evidence of a statistically significant effect favouring one drug over another. Though several analyses had high I^2, each comparison had too few studies to permit exploration of heterogeneity.

Network meta-analyses

The set of studies reporting ratios of relapse rates formed a connected network (Figure 8). In the network, all drugs were compared against placebo, but GA 40 mg thrice weekly and IFN β-1a pegylated SC 125 μg every

two weeks were not compared against other active drugs in the network. IFN β-1a 22 μg SC thrice weekly was connected to the network because of its inclusion in PRISMS 1998,[187] which also the 44 μg dose.

Random effects network meta-analysis generated estimates of each drug against placebo and against every other drug (see Table 7). Ranking of the drugs suggested that the drug with the highest cumulative probability SUCRA (surface under the cumulative ranking curve) of being the best was GA 20 mg SC once daily, followed by IFN β-1a pegylated SC 125 μg every two weeks and GA 40 mg thrice weekly, with IFN β-1a 30 μg IM once a week ranked second to last and placebo ranked last.

Findings derived from the network meta-analysis for comparisons between each drug and placebo substantially mirrored those of the pairwise comparisons, and reflected statistically significant reductions in relapse rates in patients receiving active drugs. Pairwise comparisons between drugs mostly revealed little evidence of superiority of one drug over another, though GA 20 mg SC once daily (RR=0.82, 95% CI [0.73, 0.93]), IFN β-1a 44 μg SC thrice weekly (0.85, [0.76, 0.95]) and IFN β-1b 250 μg SC every other day (0.86, [0.76, 0.97]) all produced significant reductions in relapse rate as compared to IFN β-1a 30 μg IM once a week. These pairwise comparisons from the network meta-analysis, which all included direct (i.e., head-to-head) evidence, were similar in magnitude of effect to findings from the pairwise meta-analyses, but may have benefited from a 'stabilised' heterogeneity parameter due to the assumption of equal between-studies variance.

Tests of inconsistency in the network did not suggest that direct and indirect evidence were in disagreement. A Wald test for overall inconsistency derived from a design-by-treatment interaction model was not statistically significant (p=0.38), and comparisons between the direct and indirect evidence derived from the side-splitting model did not show any statistically significant differences.

Figure 6: Pairwise meta-analyses: ARR for active vs. placebo trials in RRMS

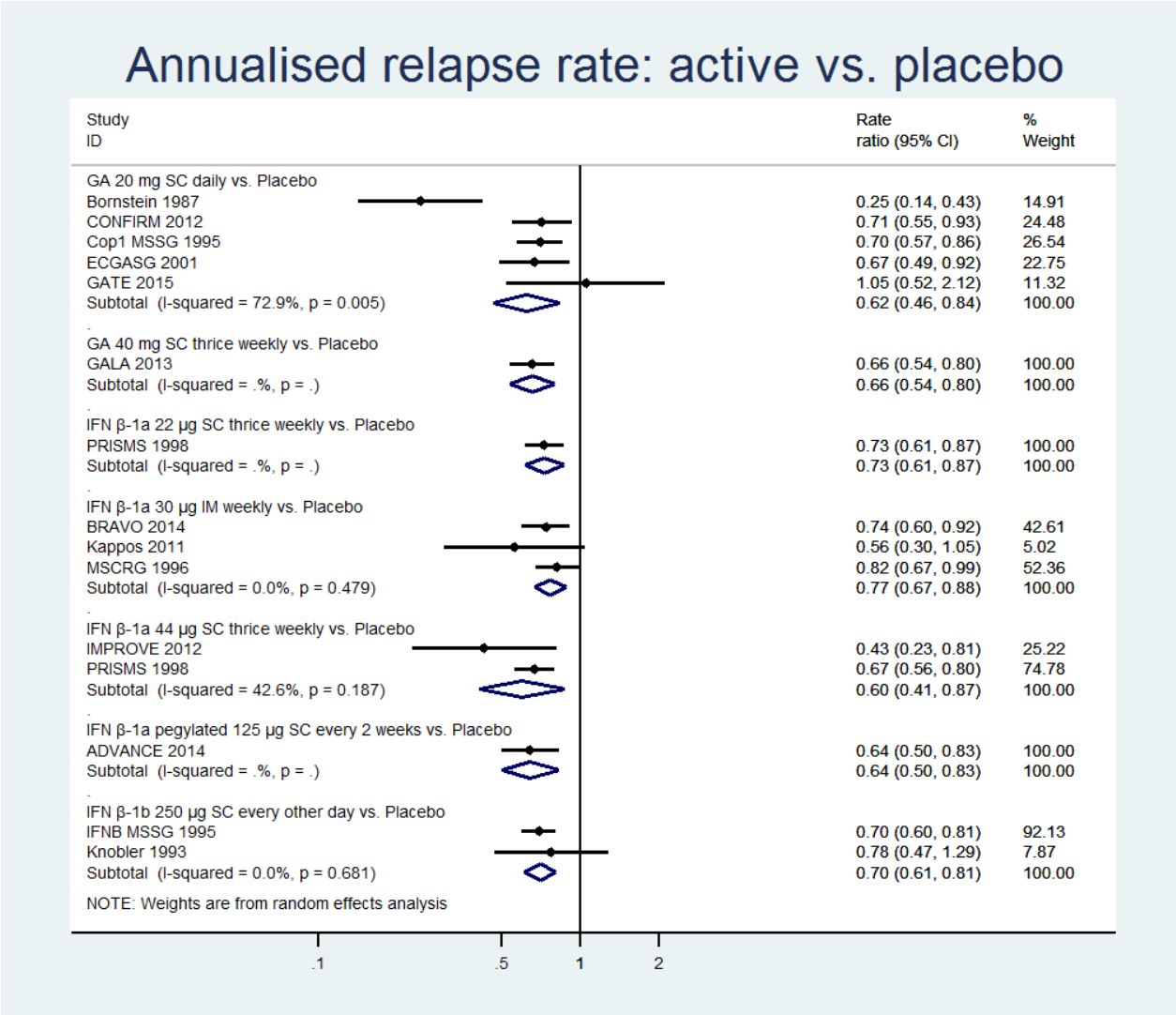


Figure 7: Pairwise meta-analyses: ARR for active vs. placebo trials in RRMS

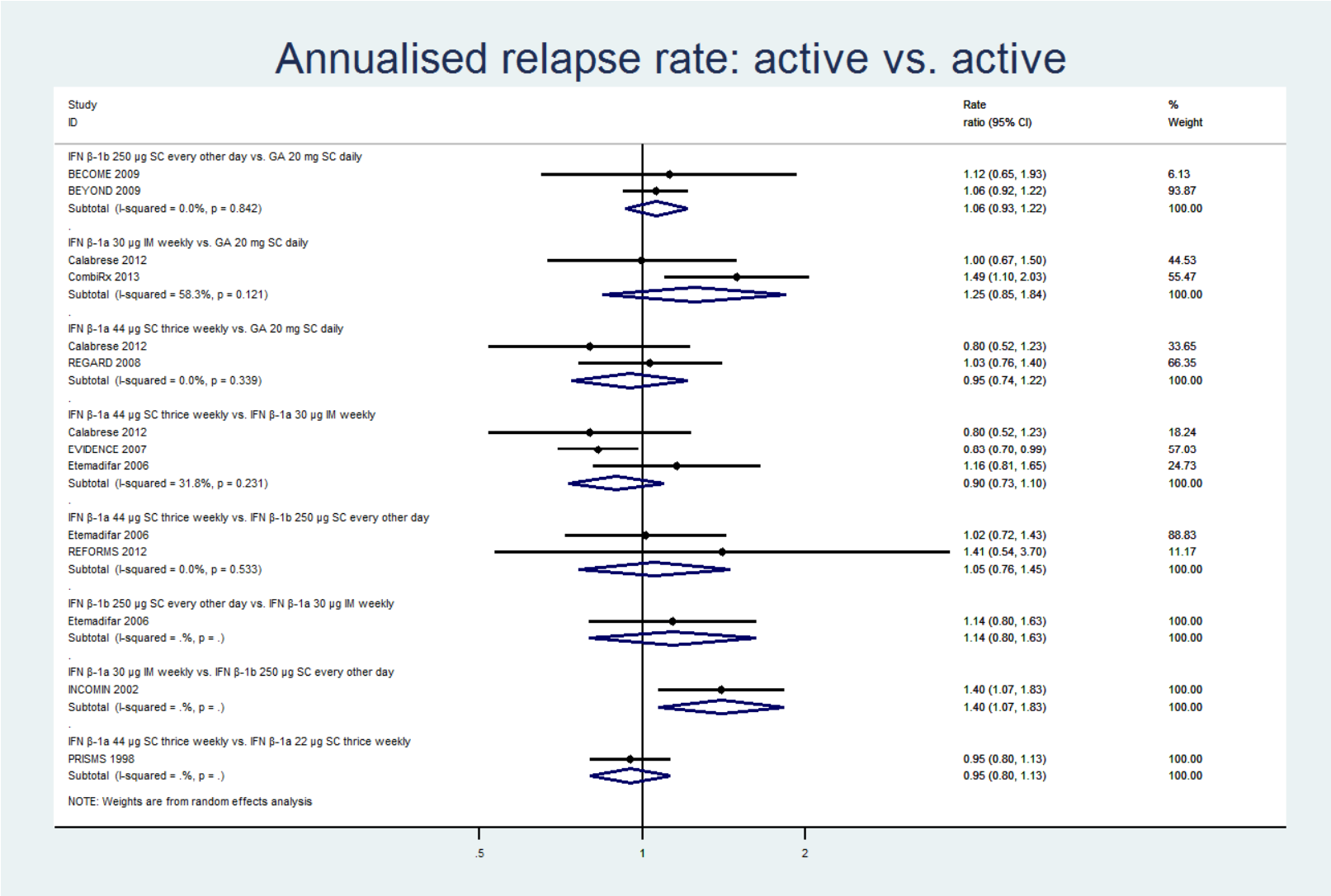


Figure 8: Network of studies, ARR in RRMS

ifn1a30: IFN β-1a 30 µg IM once a week; ifn1a44: IFN β-1a 44 µg SC three times weekly; ifn1a22: IFN β-1a 22 µg SC three times weekly; ifn1b250: IFN β-1b 250 µg SC every other day; peg: IFN β-1a pegylated 125 µg SC every two weeks; ga20: GA 20 mg SC once daily; ga40: GA 40 mg SC thrice weekly; plac: placebo

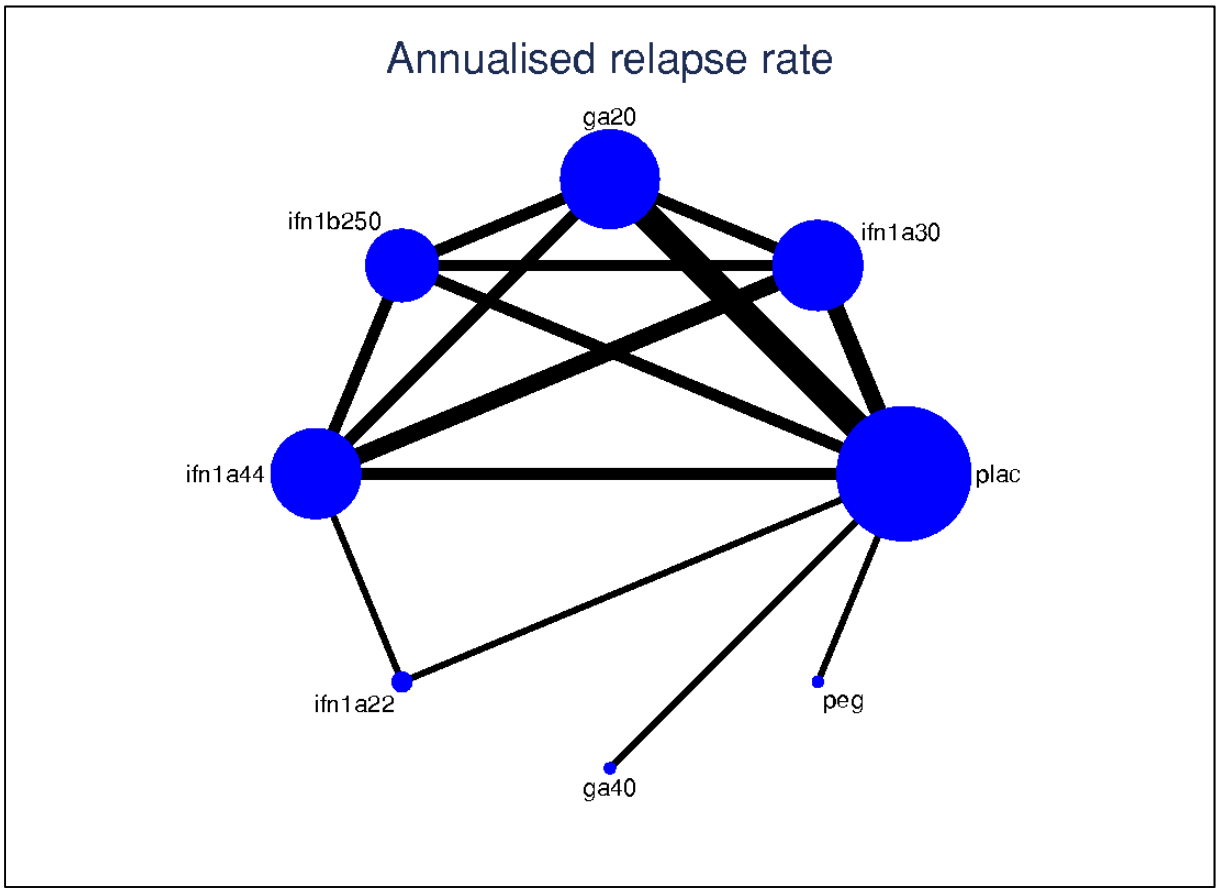


Table 7: Network meta-analysis: annualised relapse rates in RRMS

Findings are expressed as rate ratio (RR) with 95% CI.

Drug	SUCRA	GA 20 mg daily	IFN β-1a pegylated 125 µg every 2 weeks	GA 40 mg thrice weekly	IFN β-1a 44 µg SC thrice weekly	IFN β-1b 250 µg SC every other day	IFN β-1a 22 µg SC thrice weekly	IFN β-1a 30 µg IM weekly	Placebo
GA 20 mg daily	0.77		1.01 (0.77, 1.33)	1.00 (0.80, 1.24)	0.97 (0.85, 1.10)	0.95 (0.86, 1.05)	0.91 (0.76, 1.08)	0.82 (0.73, 0.92)	0.65 (0.59, 0.72)
IFN β-1a pegylated 125 µg every 2 weeks	0.73			0.98 (0.71, 1.35)	0.95 (0.72, 1.26)	0.94 (0.71, 1.23)	0.89 (0.66, 1.21)	0.81 (0.62, 1.06)	0.64 (0.50, 0.83)
GA 40 mg thrice weekly	0.70				0.97 (0.77, 1.22)	0.96 (0.77, 1.19)	0.91 (0.71, 1.17)	0.82 (0.66, 1.03)	0.66 (0.54, 0.80)
IFN β-1a 44 µg SC thrice weekly	0.64					0.99 (0.86, 1.13)	0.94 (0.80, 1.10)	0.85 (0.76, 0.95)	0.68 (0.60, 0.76)
IFN β-1b 250 µg SC every other day	0.56						0.95 (0.79, 1.14)	0.86 (0.76, 0.97)	0.69 (0.62, 0.76)
IFN β-1a 22 µg SC thrice weekly	0.43							0.91 (0.76, 1.08)	0.72 (0.61, 0.85)
IFN β-1a 30 µg IM weekly	0.18								0.80 (0.72, 0.88)
Placebo	0								
Wald test for inconsistency (χ^2, df, p)	11.71, 11, 0.38								

Table 8: Network meta-analysis: annualised relapse rates in RRMS, excluding Bornstein 1987[168]

Findings are expressed as rate ratio (RR) with 95% CI.

Drug	SUCRA	IFN β-1a pegylated 125 µg every 2 weeks	Glatiramer 40 mg thrice weekly	Glatiramer 20 mg daily	IFN β-1a 44 µg SC thrice weekly	IFN β-1b 250 µg SC every other day	IFN β-1a 22 µg SC thrice weekly	IFN β-1a 30 µg IM weekly	Placebo
IFN β-1a pegylated 125 µg every 2 weeks	0.76		0.98 (0.71, 1.35)	0.95 (0.73, 1.25)	0.94 (0.71, 1.24)	0.92 (0.70, 1.21)	0.89 (0.66, 1.20)	0.80 (0.61, 1.05)	0.64 (0.50, 0.83)
Glatiramer 40 mg thrice weekly	0.73			0.97 (0.78, 1.21)	0.96 (0.77, 1.20)	0.94 (0.75, 1.17)	0.91 (0.70, 1.17)	0.82 (0.65, 1.02)	0.66 (0.54, 0.80)
Glatiramer 20 mg daily	0.69				0.99 (0.87, 1.12)	0.98 (0.86, 1.12)	0.93 (0.78, 1.12)	0.84 (0.74, 0.95)	0.68 (0.61, 0.75)
IFN β-1a 44 µg SC thrice weekly	0.65					0.98 (0.86, 1.12)	0.94 (0.80, 1.11)	0.85 (0.76, 0.95)	0.68 (0.61, 0.76)
IFN β-1b 250 µg SC every other day	0.55						0.96 (0.80, 1.15)	0.87 (0.77, 0.98)	0.70 (0.63, 0.77)
IFN β-1a 22 µg SC thrice weekly	0.45							0.90 (0.76, 1.07)	0.72 (0.62, 0.85)
IFN β-1a 30 µg IM weekly	0.17								0.80 (0.73, 0.89)
Placebo	0.00								
Wald test for inconsistency (χ2, df, p)	12.59, 11, 0.32								

Sensitivity analyses

Several characteristics of the trials included in this network suggested that additional analyses would confirm the robustness of our findings. All of these analyses were post hoc. First, we excluded REFORMS 2012[195] from the analysis, as it was the only study were relapses were self-reported by subjects instead of documented by an examining neurologist. Effect estimates remained essentially unchanged for all pairwise comparisons.

Second, we compared findings for studies with 'true', blinded placebos against studies that did not have blinded placebos. That is, several studies did not deliver placebos via the same route of administration. Specifically, BRAVO 2014,[196] CONFIRM 2012[214] and Kappos 2011[197] did not administer placebo via the same route as the relevant IFN or GA arm in each trial. We found that effects for these drugs against placebo were robust to inclusion of a covariate in the model for trials without a blinded placebo.

Third, we noticed that Bornstein 1987[168] was an outlier in the comparison between GA 20 mg SC once daily and placebo. When we excluded this trial from the pairwise meta-analysis, the pooled rate ratio for relapses still suggested a reduction in ARR as compared to placebo (RR=0.71, 95% CI [0.62, 0.82]), with I^2 of 0%. Re-estimation of the network meta-analysis yielded a change in the SUCRA-based rankings, with GA 20 mg SC once daily now ranked third, but point estimates and confidence intervals were not substantially different in the new model (see Table 8).

9.5.13 Meta-analyses: relapse severity, moderate and severe relapses

Pairwise meta-analyses

Direct evidence from pairwise comparisons is shown in Figure 9. Each comparison was informed by one study. All drugs compared against placebo had a statistically significant beneficial effect in reducing the rate of moderate or severe relapses. In comparisons based on active drugs, there was no evidence that one dose of IFN β-1a SC thrice weekly was statistically better than the other (44 μg vs 22 μg), nor that IFN β-1b 250 μg SC every other day was different from GA 20 mg SC once daily. GA 40 mg thrice weekly, IFN β-1a 30 μg IM once a week and IFN β-1a pegylated SC 125 μg every two weeks were not represented in this analysis.

Network meta-analyses

The set of studies reporting ratios of relapse rates for moderate and severe relapses formed a connected network (Figure 10). In the network, direct evidence for GA 20 mg SC once daily was only against another active drug, IFN β-1b 250 μg SC every other day.

Because of the shape of the network, in which there was no opportunity for inconsistency and in which no direct comparison was informed by more than one trial, the model was estimated using fixed effects instead of random effects as in the protocol. Ranking of drugs suggested that GA 20 mg SC once daily was best, followed by IFN β-1b 250 μg SC every other day, IFN β-1a SC thrice weekly (44 μg and 22 μg), and placebo ranked last (see Table 9).

Figure 9: Pairwise estimates: ARR for moderate or severe relapses in RRMS

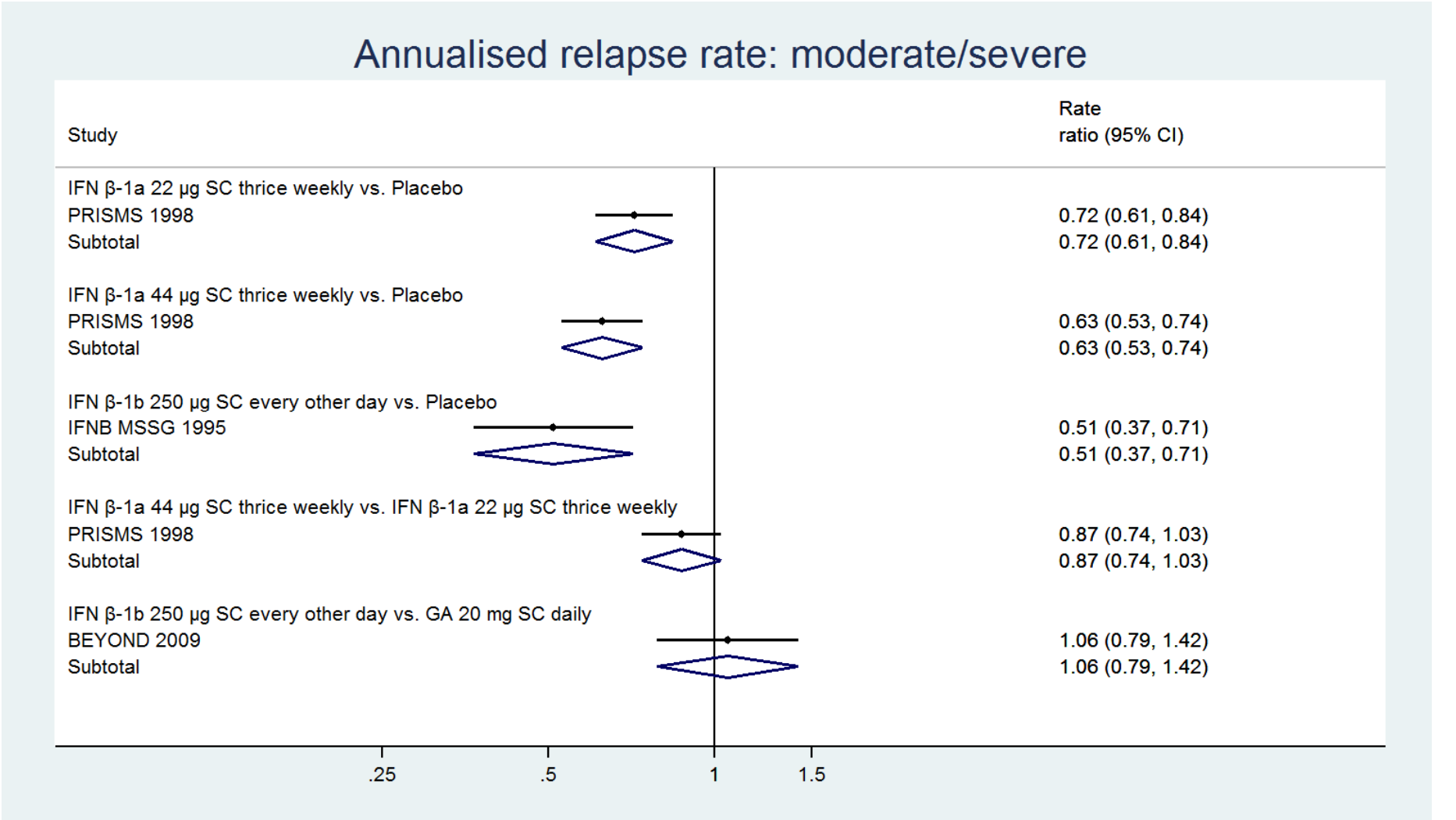


Figure 10: Network of studies, ARR for moderate or severe relapses in RRMS

ifn1a44: IFN β-1a 44 µg SC three times weekly; ifn1a22: IFN β-1a 22 µg SC three times weekly; ifn1b250: IFN β-1b 250 µg SC every other day; ga20: GA 20 mg SC once daily; plac: placebo

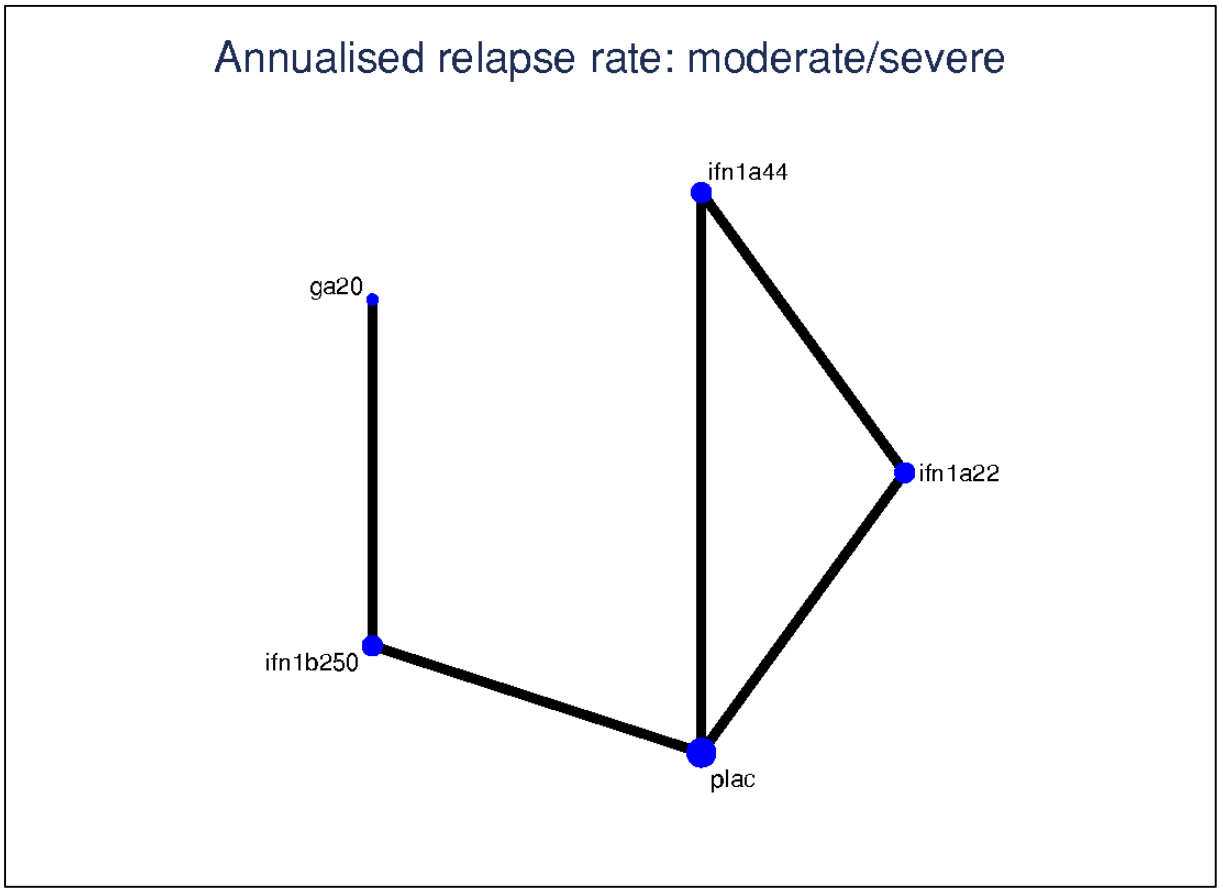


Table 9: Network meta-analysis: annualised relapse rate, moderate/severe relapses in RRMS

Findings are expressed as RR (95% CI)

Drug	SUCRA	GA 20 mg daily	IFN β-1b 250 µg SC every other day	IFN β-1a 44 µg SC thrice weekly	IFN β-1a 22 µg SC thrice weekly	Placebo
GA 20 mg daily	0.85		0.95 (0.70, 1.27)	0.77 (0.48, 1.24)	0.68 (0.42, 1.08)	0.48 (0.31, 0.76)
IFN β-1b 250 µg SC every other day	0.80			0.82 (0.56, 1.19)	0.71 (0.49, 1.03)	0.51 (0.37, 0.71)
IFN β-1a 44 µg SC thrice weekly	0.57				0.87 (0.74, 1.03)	0.63 (0.53, 0.74)
IFN β-1a 22 µg SC thrice weekly	0.28					0.72 (0.61, 0.84)
Placebo	0.00					

Findings derived from the network meta-analysis for comparisons between each drug and placebo were similar to comparisons against placebo from the direct evidence, as would be expected. In an indirect comparison, GA 20 mg SC once daily reduced the rate of moderate and severe relapses as compared to placebo (RR=0.48, 95% CI [0.31, 0.76]). Pairwise comparisons between active drugs did not yield evidence of superiority of any one drug over another.

Because there was not the possibility for inconsistency in the network, we did not test for it.

9.5.14 Meta-analyses: relapse severity, steroid-treated relapses

Pairwise meta-analysis

Direct evidence from comparisons against placebo is shown in Figure 11. Each comparison was informed by one study. All drugs that were compared against placebo showed a significant effect in reducing the rate of steroid-treated relapses. In head-to-head comparisons between active drugs, IFN β-1a 44 µg SC thrice weekly produced a greater reduction in steroid-treated relapses than the 22 µg dose of the same drug (RR=0.77, 95% CI [0.67, 0.89]) and as compared to IFN β-1a 30 µg IM once a week (0.68, [0.51, 0.91]). Pairwise comparisons between IFN β-1a 30 µg IM once a week and IFN β-1b 250 µg SC every other day, and between IFN β-1a 44 µg SC thrice weekly and GA 20 mg SC once daily, did not show statistical evidence of superiority. IFN β-1a pegylated SC 125 µg every two weeks was not included in this analysis.

Network meta-analyses

The set of studies reporting ratios of steroid-treated relapse rates formed a connected network (Figure 12). In the network, each comparison was informed by one study, but there were closed loops between studies, suggesting the possibility of inconsistency. Because in this parametrisation of the model inconsistency is regarded as a source of heterogeneity—even though there is no potential for heterogeneity in any of the comparisons informed by direct evidence—we estimated the model as both a fixed effects and a random effects model.

Numerical estimates of intervention effectiveness were not meaningfully different between the random and fixed effects models (see Table 10). However, the random effects model did not support that IFN β-1b 250 µg SC every other day significantly reduces the rate of steroid-treated relapses (fixed effects RR=0.62, 95% CI [0.40, 0.98]; random effects 0.64, [0.36, 1.14]). The random effects model also did not support the superiority

of any one drug against another, except for IFN β-1a 44 μg SC thrice weekly over IFN β-1a 30 μg IM once a week (0.68, [0.48, 0.97]). However, in the fixed effects model, IFN β-1a 44 μg SC thrice weekly improved over both IFN β-1a 30 μg IM once a week (0.68, [0.51, 0.91]) and IFN β-1a 22 μg SC thrice weekly (0.79, [0.68, 0.91]), both of which were comparisons informed by direct evidence. GA 20 mg SC once daily also improved over both IFN β-1a 30 μg IM once a week (0.67, [0.47, 0.95]) and IFN β-1a 22 μg SC thrice weekly (0.77, [0.61, 0.98]), though neither comparison was informed by direct evidence.

Because the overall Wald test of inconsistency did not provide evidence of a difference between direct and indirect evidence (p=0.20), the fixed effects model may be preferable.

Figure 11: Pairwise estimates: ARR for steroid-treated relapses in RRMS

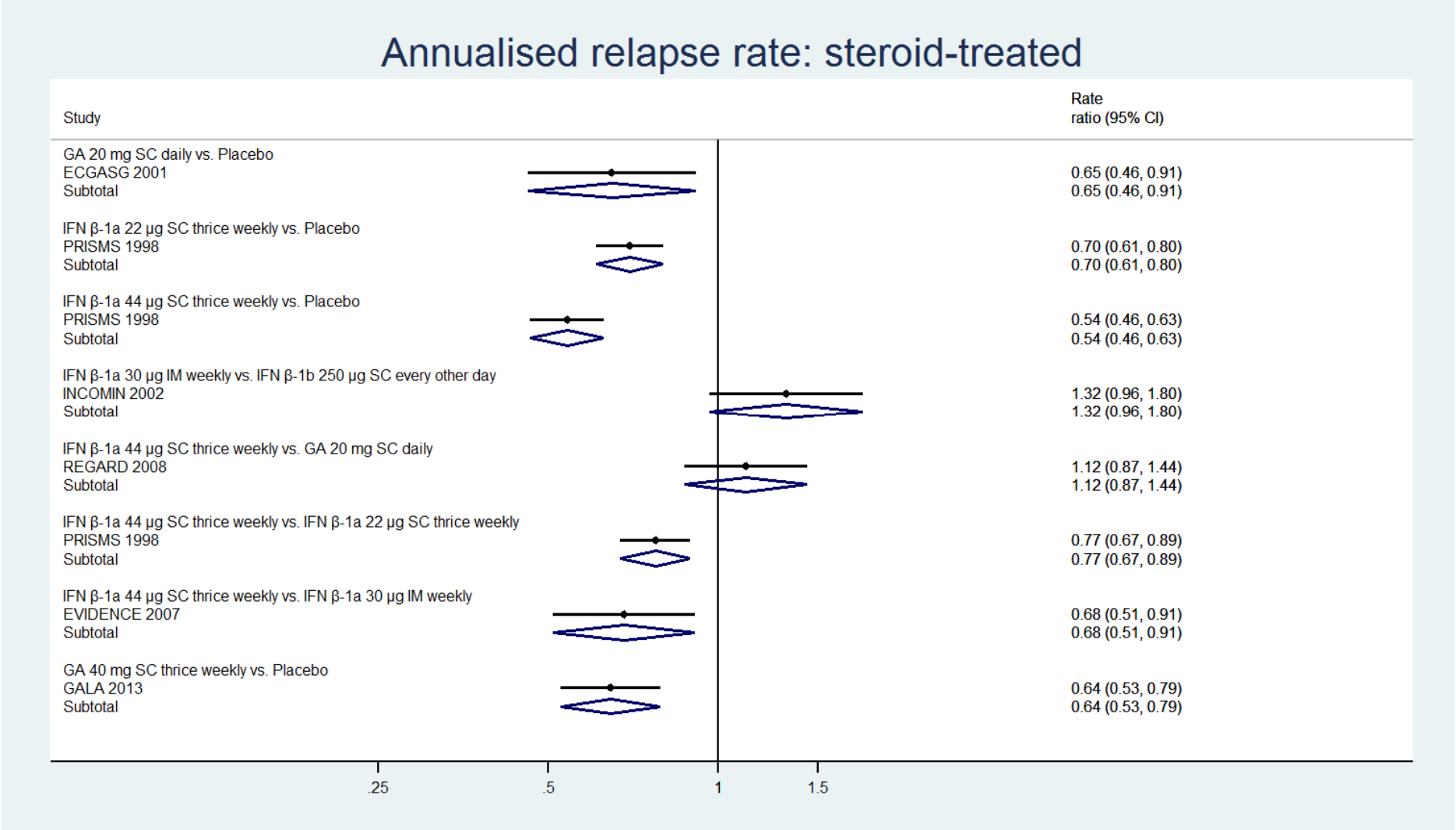


Figure 12: Network of studies, ARR for steroid-treated relapses in RRMS

ifn1a30: IFN β-1a 30 µg IM once a week; ifn1a44: IFN β-1a 44 µg SC three times weekly; ifn1a22: IFN β-1a 22 µg SC three times weekly; ifn1b250: IFN β-1b 250 µg SC every other day; ga20: GA 20 mg SC once daily; ga40: GA 40 mg SC thrice weekly; plac: placebo

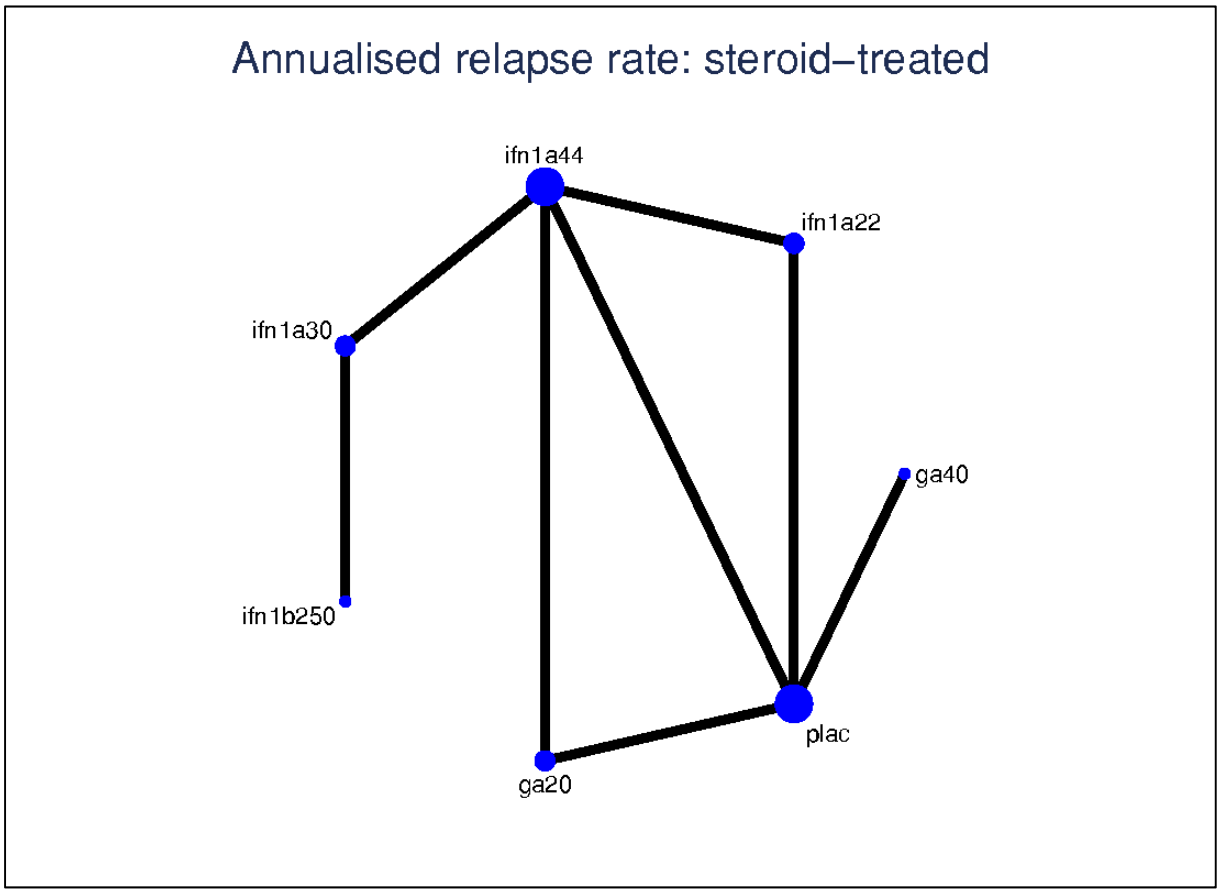


Table 10: Network meta-analysis: annualised relapse rate, steroid-treated relapses in RRMS

Findings are expressed as RR (95% CI)

Drug	**Fixed effects model**							
	SUCRA	**Glatiramer 20 mg daily**	**IFN β-1a 44 µg SC thrice weekly**	**IFN β-1b 250 µg SC every other day**	**Glatiramer 40 mg thrice weekly**	**IFN β-1a 22 µg SC thrice weekly**	**IFN β-1a 30 µg IM weekly**	**Placebo**
GA 20 mg daily	0.85		0.98 (0.80, 1.21)	0.88 (0.55, 1.41)	0.85 (0.63, 1.15)	0.77 (0.61, 0.98)	0.67 (0.47, 0.95)	0.55 (0.44, 0.68)
IFN β-1a 44 µg SC thrice weekly	0.83			0.89 (0.58, 1.37)	0.87 (0.68, 1.11)	0.79 (0.68, 0.91)	0.68 (0.51, 0.91)	0.56 (0.48, 0.64)
IFN β-1b 250 µg SC every other day	0.64				0.97 (0.59, 1.58)	0.88 (0.56, 1.38)	0.76 (0.56, 1.04)	0.62 (0.40, 0.98)
GA 40 mg thrice weekly	0.56					0.91 (0.71, 1.16)	0.79 (0.54, 1.15)	0.64 (0.53, 0.79)
IFN β-1a 22 µg SC thrice weekly	0.40						0.86 (0.63, 1.19)	0.71 (0.62, 0.81)
IFN β-1a 30 µg IM weekly	0.20							0.82 (0.59, 1.13)
Placebo	0.02							
Wald test for inconsistency (χ^2, df, p)	1.65, 1, 0.20							
Drug	**Random effects model**							
	SUCRA	**GA 20 mg daily**	**IFN β-1a 44 µg SC thrice weekly**	**IFN β-1b 250 µg SC every other day**	**GA 40 mg thrice weekly**	**IFN β-1a 22 µg SC thrice weekly**	**IFN β-1a 30 µg IM weekly**	**Placebo**
GA 20 mg daily	0.82		0.98 (0.75, 1.29)	0.88 (0.49, 1.58)	0.87 (0.57, 1.34)	0.78 (0.56, 1.10)	0.67 (0.43, 1.05)	0.56 (0.41, 0.77)
IFN β-1a 44 µg SC thrice weekly	0.81			0.89 (0.53, 1.50)	0.89 (0.60, 1.31)	0.80 (0.62, 1.03)	0.68 (0.48, 0.97)	0.57 (0.44, 0.74)
IFN β-1b 250 µg SC every other day	0.64				0.99 (0.52, 1.90)	0.89 (0.50, 1.58)	0.76 (0.52, 1.11)	0.64 (0.36, 1.14)
GA 40 mg thrice weekly	0.59					0.90 (0.61, 1.32)	0.67 (0.43, 1.05)	0.64 (0.48, 0.86)
IFN β-1a 22 µg SC thrice weekly	0.44						0.85 (0.55, 1.32)	0.72 (0.56, 0.92)
IFN β-1a 30 µg IM weekly	0.23							0.84 (0.54, 1.30)
Placebo	0.06							
Wald test for inconsistency (χ2, df, p)	1.63, 1, 0.20							

9.5.15 Meta-analyses: time to disability progression confirmed at three months

Pairwise meta-analyses

Direct evidence from comparisons is shown in Figure 13. Only one comparison, IFN β-1a 44 μg SC thrice weekly vs. placebo, included more than one study. GA 40 mg thrice weekly was not represented in this analysis.

Comparison of drugs against placebo showed a mixed pattern of results. GA 20 mg SC once daily (HR=0.79, 95% CI [0.60, 1.05]), IFN β-1a 30 μg IM once a week (0.74, [0.51, 1.08]), and IFN β-1b 250 μg SC every other day (0.71, [0.48, 1.06]) did not show evidence of delaying disability progression. However, IFN β-1a in both doses—44 μg SC thrice weekly (0.62, [0.43, 0.90]) and 22 μg SC thrice weekly (0.68, [0.48, 0.97])—and IFN β-1a pegylated SC 125 μg every two weeks (0.62, [0.40, 0.97]) did show evidence of delaying disability progression. None of the three direct comparisons between active drugs suggested a benefit of one over another.

Network meta-analyses

The set of studies reporting hazard ratios for time to disability progression confirmed at three months formed a connected network (see Figure 14). In the network, all active drugs were compared against placebo, and three comparisons between active drugs were present as well.

The network meta-analysis, which was estimated with random effects per the protocol, generated estimates of each drug against placebo and against every other drug (see Table 11). Ranking of the drugs suggested that the drug with the highest cumulative probability of being the best was IFN β-1a 44 μg SC thrice weekly, followed by IFN β-1a pegylated SC 125 μg every two weeks and IFN β-1a 22 μg SC thrice weekly, with IFN β-1b 250 μg SC every other day ranked second to last and placebo ranked last.

Comparisons for active drugs vs. placebo were similar between the network meta-analysis and the pairwise meta-analyses. Notably, additional information from indirect comparisons yielded a more precise estimate of effectiveness for both IFN β-1a 30 μg IM once a week vs placebo (HR=0.73, 95% CI [0.53, 1.00], p=0.0499) and GA 20 mg SC once daily (0.76, [0.60, 0.97]). Comparisons between active drugs estimated from the network meta-analysis did not indicate than any one drug was statistically better than the others, as all pairwise comparisons were not statistically significant.

Tests of inconsistency in the network did not suggest that direct and indirect evidence were in disagreement. An overall Wald test derived from a design-by-treatment interaction model returned a non-significant results (p=0.84), and comparisons between the direct and indirect evidence derived from the side-splitting model did not show any statistically significant differences.

Figure 13: Pairwise meta-analyses: time to disability progression confirmed at 3 months in RRMS

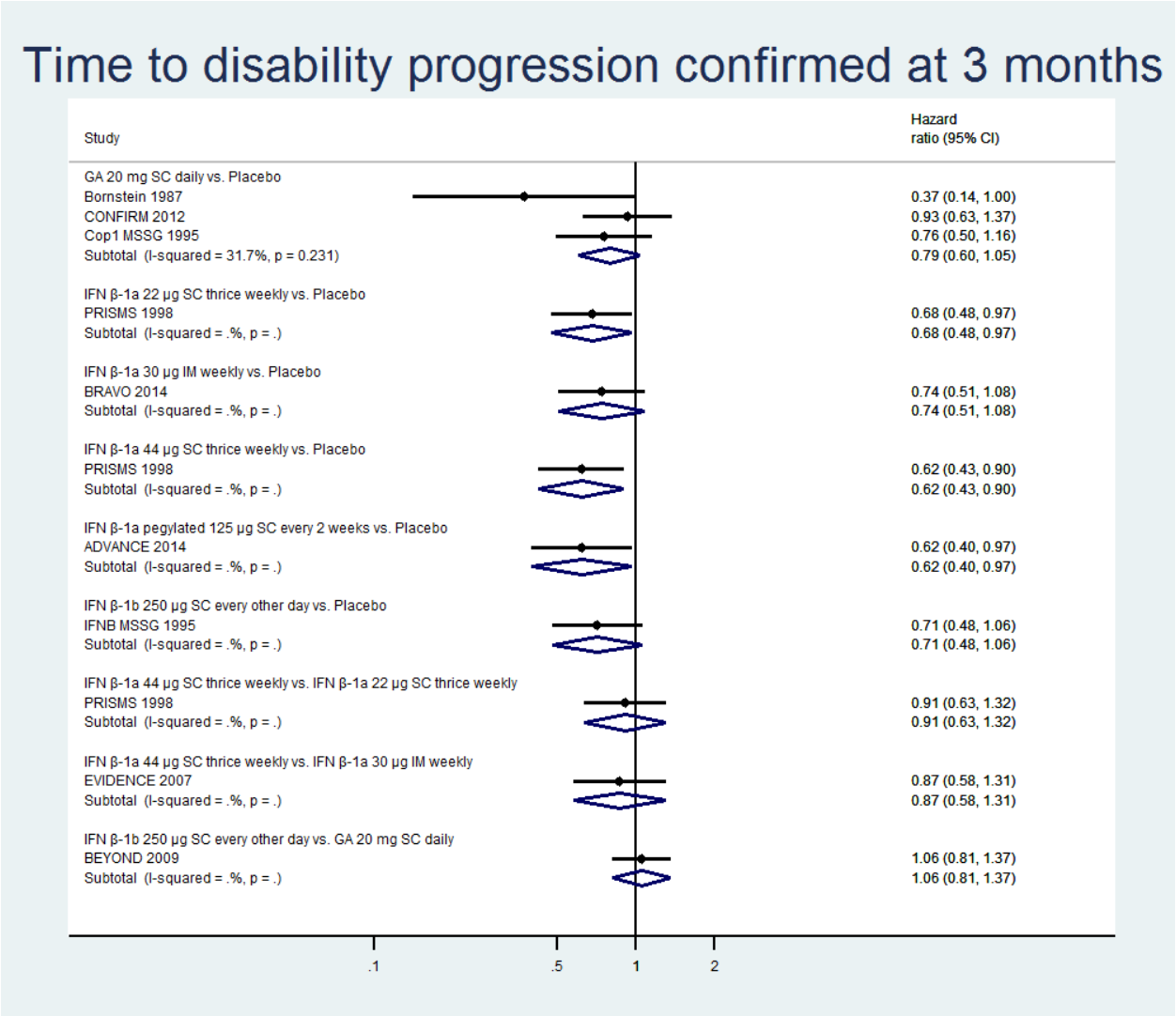


Figure 14: Network of studies, time to disability progression confirmed at 3 months in RRMS

ifn1a30: IFN β-1a 30 µg IM once a week; ifn1a44: IFN β-1a 44 µg SC three times weekly; ifn1a22: IFN β-1a 22 µg SC three times weekly; ifn1b250: IFN β-1b 250 µg SC every other day; peg: IFN β-1a pegylated 125 µg SC every two weeks; ga20: GA 20 mg SC once daily; plac: placebo

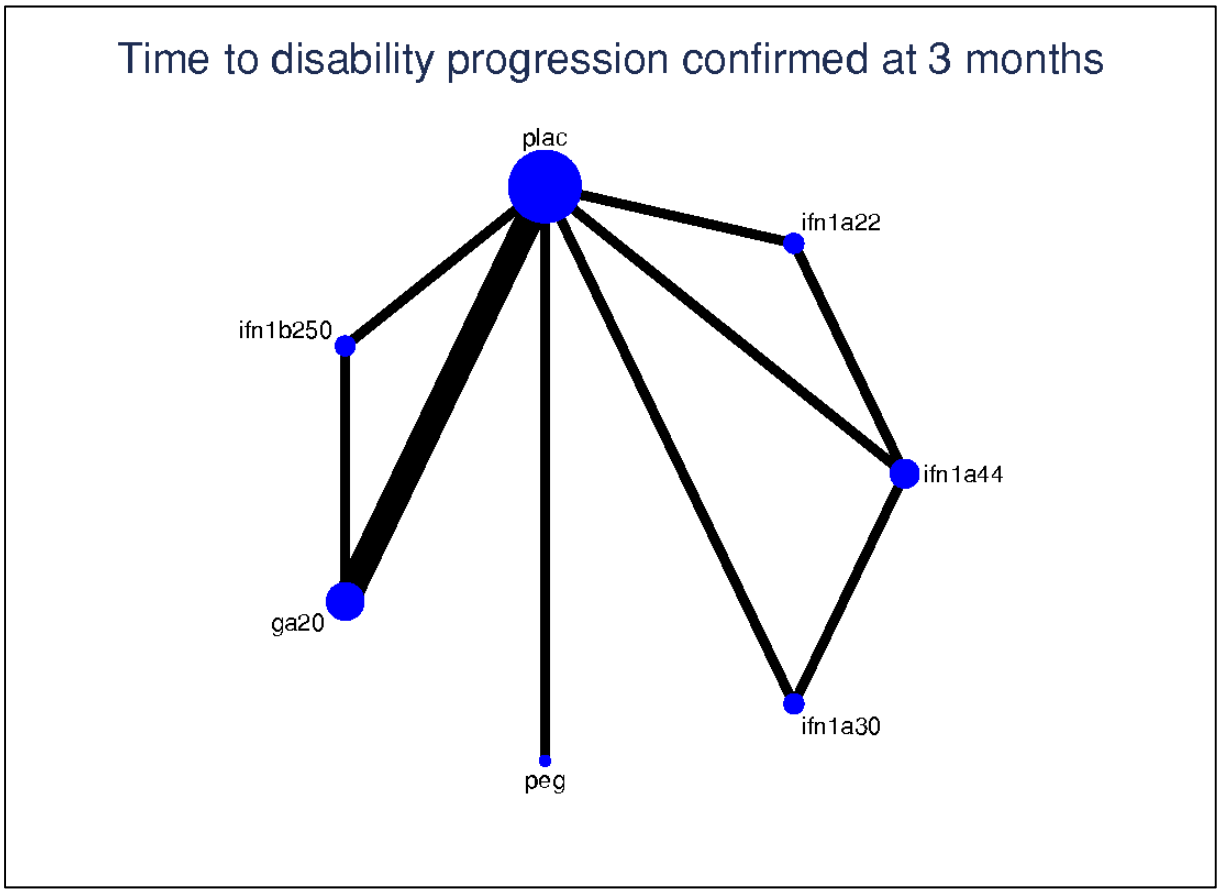


Table 11: Network meta-analysis: time to disability progression confirmed at 3 months in RRMS

Findings are labelled as HR (95% CI).

Drug	SUCRA	IFN β-1a 44 µg SC thrice weekly	IFN β-1a pegylated 125 µg every 2 weeks	IFN β-1a 22 µg SC thrice weekly	IFN β-1a 30 µg IM weekly	GA 20 mg daily	IFN β-1b 250 µg SC every other day	Placebo
IFN β-1a 44 µg SC thrice weekly	0.77		1.01 (0.59, 1.74)	0.92 (0.65, 1.30)	0.86 (0.62, 1.19)	0.82 (0.56, 1.22)	0.81 (0.53, 1.22)	0.63 (0.46, 0.86)
IFN β-1a pegylated 125 µg every 2 weeks	0.75			0.91 (0.52, 1.59)	0.85 (0.49, 1.46)	0.81 (0.49, 1.34)	0.80 (0.47, 1.34)	0.62 (0.40, 0.97)
IFN β-1a 22 µg SC thrice weekly	0.62				0.94 (0.62, 1.42)	0.90 (0.59, 1.36)	0.88 (0.57, 1.36)	0.68 (0.49, 0.96)
IFN β-1a 30 µg IM weekly	0.50					0.96 (0.65, 1.42)	0.94 (0.62, 1.43)	0.73 (0.53, 1.00)*
GA 20 mg daily	0.44						0.98 (0.78, 1.24)	0.76 (0.60, 0.97)
IFN β-1b 250 µg SC every other day	0.39							0.78 (0.59, 1.02)
Placebo	0.02							
Wald test for inconsistency (χ2, df, p)	0.35, 2, 0.84							

9.5.16 Meta-analyses: time to disability progression confirmed at six months

Pairwise meta-analyses

Direct evidence from comparisons is shown in Figure 15. All comparisons were based on a single study, except for IFN β-1a 30 μg IM once a week as compared to placebo. GA 40 mg thrice weekly was not represented in this analysis.

Three drugs were compared against placebo. GA 20 mg SC once daily did not delay confirmed disability progression as compared to placebo, but IFN β-1a 30 μg SC once weekly (HR=0.66, 95% CI [0.47, 0.92]) and IFN β-1a pegylated 125 μg every two weeks (0.46, [0.26, 0.81]) did. Of the three comparisons between active drugs, only IFN β-1a 30 μg IM once a week yielded a significant improvement, when compared to IFN β-1b 250 μg SC every other day.

Network meta-analysis

The set of studies reporting hazard ratios for time to disability progression confirmed at six months formed a connected network (see Figure 16). In the network, IFN β-1b 250 μg SC every other day and IFN β-1a 44 μg SC thrice weekly are not compared to placebo, but only to other active drugs.

The network meta-analysis, which was estimated with random effects per the protocol, generated estimates of each drug against placebo and against every other drug (see Table 12). Ranking of the drugs suggested that the drug with the highest cumulative probability of being the best was IFN β-1b 250 μg SC every other day, followed by IFN β-1a pegylated 125 μg every two weeks, IFN β-1a 44 μg SC thrice weekly and IFN β-1a 30 μg IM once a week. GA 20 mg SC once daily was ranked second to last and placebo was ranked last.

When compared against placebo in the network meta-analysis, GA 20 mg SC once daily had a similar estimate of effectiveness (HR=0.82, 95% CI [0.53, 1.26]) as compared to the direct evidence, as did IFN β-1a 30 μg IM once a week (0.68, [0.49, 0.94]) and IFN β-1a pegylated 125 μg every two weeks (0.46, [0.26, 0.81]). Both IFN β-1a 44 μg SC thrice weekly (0.47, [0.24, 0.93]) and IFN β-1b 250 μg SC every other day (0.34, [0.18, 0.63]) showed evidence of delaying disability progression as compared to placebo. However, both of these estimates are based solely on indirect evidence, and findings from INCOMIN 2002,[194] which informed the contrast between IFN β-1b 250 μg SC every other day and IFN β-1a 30 μg IM once a week, relied on a hazard ratio estimated from summary statistics.

Comparisons between active drugs estimated from the NMA suggested that IFN β-1b 250 μg SC every other day is superior both to IFN β-1a 30 μg IM once a week (HR=0.50, 95% CI [0.29, 0.87]) and to GA 20 mg SC once daily (0.41, [0.21, 0.83]). The comparison between IFN β-1b 250 μg SC every other day and GA 20 mg SC once daily in particular was greater in magnitude than direct evidence suggested. No other comparisons between active drugs yielded statistically significant evidence of superiority of one drug over others.

Tests of inconsistency in the network did not suggest that direct and indirect evidence disagreed to a statistically significant level; however, the network was sparse and only one comparison included more than one study. An overall Wald test of inconsistency returned a statistically non-significant result (p=0.38).

Figure 15: Pairwise meta-analyses: time to disability progression confirmed at 6 months in RRMS

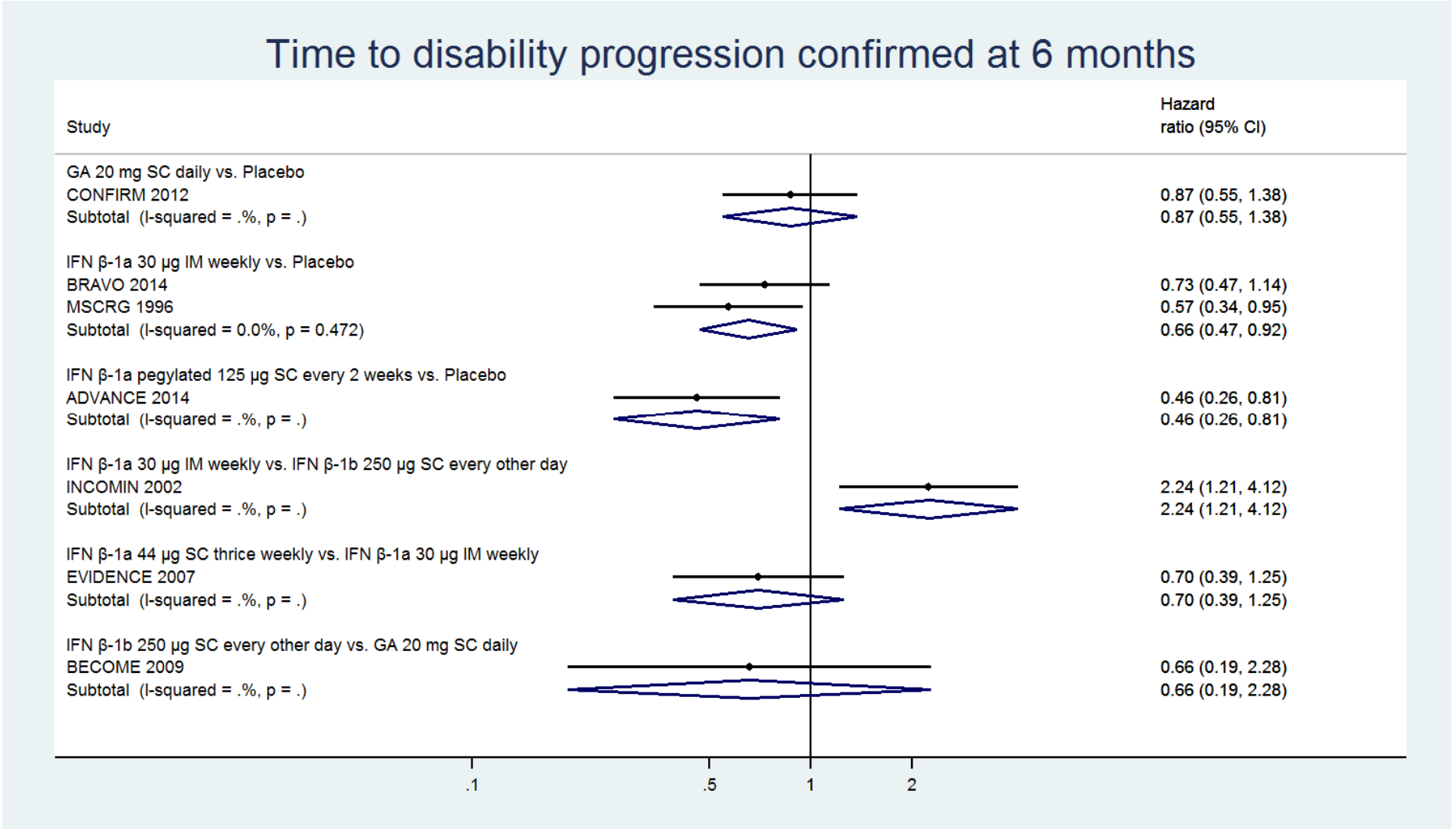


Figure 16: Network of studies, time to disability progression confirmed at 6 months in RRMS

ifn1a30: IFN β-1a 30 µg IM once a week; ifn1a44: IFN β-1a 44 µg SC three times weekly; ifn1b250: IFN β-1b 250 µg SC every other day; peg: IFN β-1a pegylated 125 µg SC every two weeks; ga20: GA 20 mg SC once daily; plac: placebo

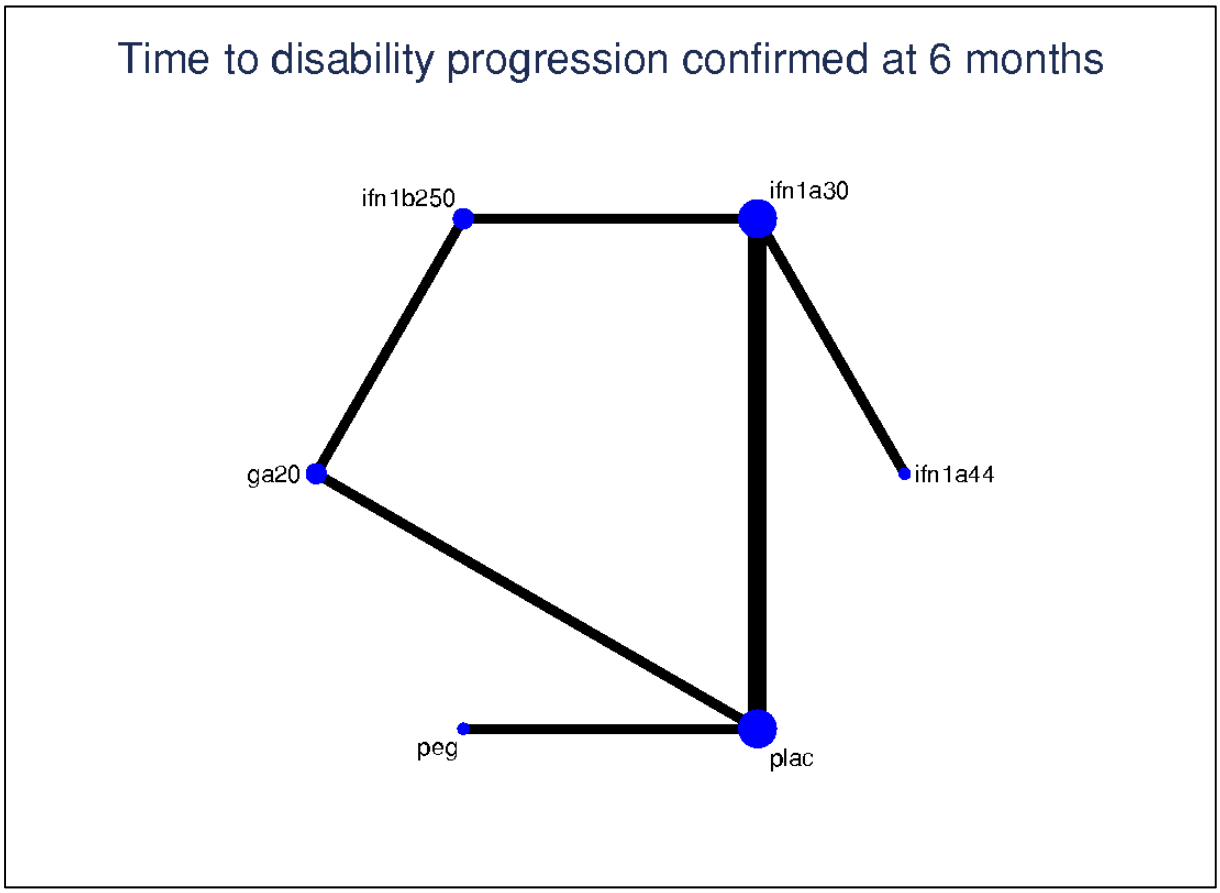


Table 12: Network meta-analysis: time to disability progression confirmed at 6 months in RRMS

Findings are presented as HR (95% CI).

Drug	**SUCRA**	**IFN β-1b 250 µg SC every other day**	**IFN β-1a pegylated 125 µg every 2 weeks**	**IFN β-1a 44 µg SC thrice weekly**	**IFN β-1a 30 µg IM weekly**	**Glatiramer 20 mg daily**	**Placebo**
IFN β-1b 250 µg SC every other day	0.90		0.74 (0.32, 1.71)	0.71 (0.32, 1.60)	0.50 (0.29, 0.87)	0.42 (0.21, 0.83)	0.34 (0.18, 0.63)
IFN β-1a pegylated 125 µg every 2 weeks	0.71			0.97 (0.40, 2.33)	0.68 (0.35, 1.31)	0.56 (0.28, 1.15)	0.46 (0.26, 0.81)
IFN β-1a 44 µg SC thrice weekly	0.70				0.70 (0.39, 1.25)	0.58 (0.27, 1.27)	0.47 (0.24, 0.93)
IFN β-1a 30 µg IM weekly	0.40					0.83 (0.49, 1.41)	0.68 (0.49, 0.94)
Glatiramer 20 mg daily	0.25						0.82 (0.53, 1.26)
Placebo	0.05						
Wald test for inconsistency (χ2, df, p)	1, 0.77, 0.38						

9.5.17 Meta-analyses: adverse events

Summary of adverse events meta-analyses

Full results for pairwise meta-analyses of AEs are available on request. Though the diversity and heterogeneity of AEs precludes detailed examination of each, several trends were apparent across pairwise comparisons.

- Comparing IFN β-1a 30µg (Avonex) vs. equivalent placebo, the IFN β-1a 30 µg was associated with more chills, flu-like symptoms, neutralising antibodies and myalgia.
- Comparing IFN β-1a 30µg (Avonex) vs. IFN β-1a 44 µg (Rebif), IFN β-1a 44 µg was associated with more injection site reactions, liver disorders, neutralising antibodies and white blood cell abnormalities, while the 30µg was associated with more fatigue.
- Comparing IFN β-1a 30µg (Avonex) vs. IFN β-1b (Betaferon/Extavia), the IFN β-1b was associated with more injection reactions and neutralising antibodies.
- Comparing IFN β-1a 30 µg (Avonex) vs. GA (Copaxone), there were no significant differences in AEs.
- Comparing IFN β-1a 44 µg (Rebif) vs. placebo, IFN β-1a 44 µg was associated with more injection reactions, flu-like illness, liver disorders, granulocytopenia, leucopenia, lymphopenia and neutralising antibodies
- Comparing IFN β-1a 44 µg (Rebif) vs. IFN β-1b (Betaferon/Extavia), the IFN β-1a 44 µg was associated with more ALT disorders and the IFNβ1b with more injection pain.
- Comparing IFN β-1a 44µg (Rebif) vs. GA (Copaxone), the IFN β-1a 44 µg was associated with more liver enzyme disorders, neutralising antibodies, headache, flu-like illness and myalgia, and the glatiramer with more injection reactions, immediate post-injection reactions and binding antibodies.
- Comparing IFN β-1b (Betaferon/Extavia) vs. placebo, IFN β-1b was associated with more injection site inflammation and neutralising antibodies.
- Comparing IFN β-1b (Betaferon/Extavia) vs. GA (Copaxone), IFN β-1b was associated with more flu-like symptoms, insomnia and disordered liver enzymes, and glatiramer with more injection site reactions, itching, pain, inflammation and induration, and immediate post-injection reactions.
- Comparing GA (Copaxone) vs. equivalent placebo, glatiramer was associated with more injection-site induration, itching, mass, erythema, pain, inflammation, and reactions, and more immediate post-injection systemic reactions.
- Comparing pegylated IFN β-1a (Plegridy) vs. placebo, pegylated IFN β-1a was associated with more injection-site erythema, pain, itching, chills and/or fever, headache, flu-like syndrome, myalgia, pyrexia, any AE possibly related to drug, patients who discontinued study due to AE and severe AE.

Discontinuation due to adverse events: modal follow-up

Pairwise meta-analyses

Pairwise meta-analyses for discontinuation due to AEs combined across studies at the modal follow-up are presented in Figure 17. The modal follow-up was approximately 24 months, and thus we included studies with intended follow-up around this point. We included 12 estimates in these meta-analyses. There was no visual

evidence of a systematic difference based on the strict definition of the outcome. In every pairwise meta-analysis, confidence intervals were wide, as would be expected. Three pooled estimates relied on multiple studies: GA 20 mg SC once daily vs. placebo, IFN β-1a 30 μg IM once a week vs. placebo, and IFN β-1b 250 μg SC every other day vs. GA 20 mg SC once daily. There was no evidence in this analysis for GA 40 mg SC three times weekly or IFN β-1a pegylated 125 μg every two weeks.

Despite visual evidence suggesting that discontinuation due to AEs was more likely in study arms testing active drugs as compared to study arms testing placebo, almost all individual study estimates and pooled estimates did not suggest that, to a statistically significant level, discontinuation was more likely in trial arms corresponding to one drug over another. The one exception was IFNB MSSG 1995, from which we used 24-month data.[208] In this study, which tested IFN β-1b 250 μg SC every other day against placebo, patients receiving the study drug were more likely to withdraw from the study due to an AE (risk ratio=9.92, 95% CI [1.29, 76.32]).

Network meta-analysis

The set of studies included in this analysis formed a connected network (see Figure 18). All drugs were compared to placebo. GA 40 mc SC three times weekly and IFN β-1a pegylated 125 μg every two weeks were not included in this analysis.

The NMA, which was estimated with random effects, generated estimates of each drug against placebo and against every other drug (see Table 13). Because confidence intervals were wide in pairwise, direct meta-analyses, confidence intervals were wide in the NMAs and estimates as compared to placebo were often numerically different. The NMA did not offer statistical evidence that any one drug was more likely to result in discontinuation due to AEs as compared to another. Based on SUCRAs, IFN β-1b 250 μg SC every other day was ranked highest for discontinuation due to AEs, followed by IFN β-1a 44 μg SC thrice weekly. Placebo was ranked last.

Figure 17: Pairwise meta-analyses: discontinuation due to AEs at 24 months in RRMS

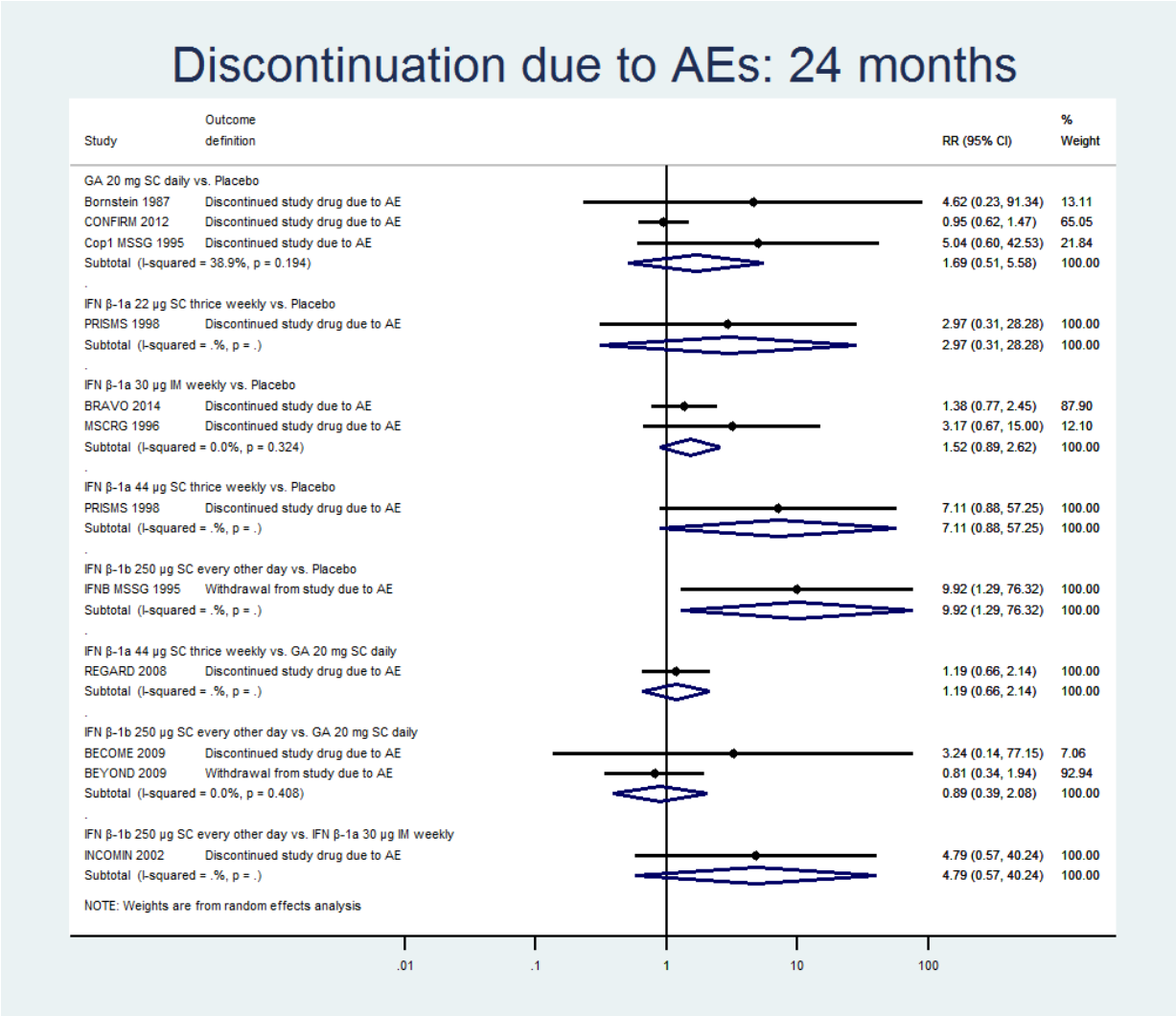


Figure 18: Network of studies, discontinuation due to AEs at 24 months in RRMS

ifn1a30: IFN β-1a 30 µg IM once a week; ifn1a44: IFN β-1a 44 µg SC three times weekly; ifn1a22: IFN β-1a 22 µg SC three times weekly; ifn1b250: IFN β-1b 250 µg SC every other day; ga20: GA 20 mg SC once daily; plac: placebo

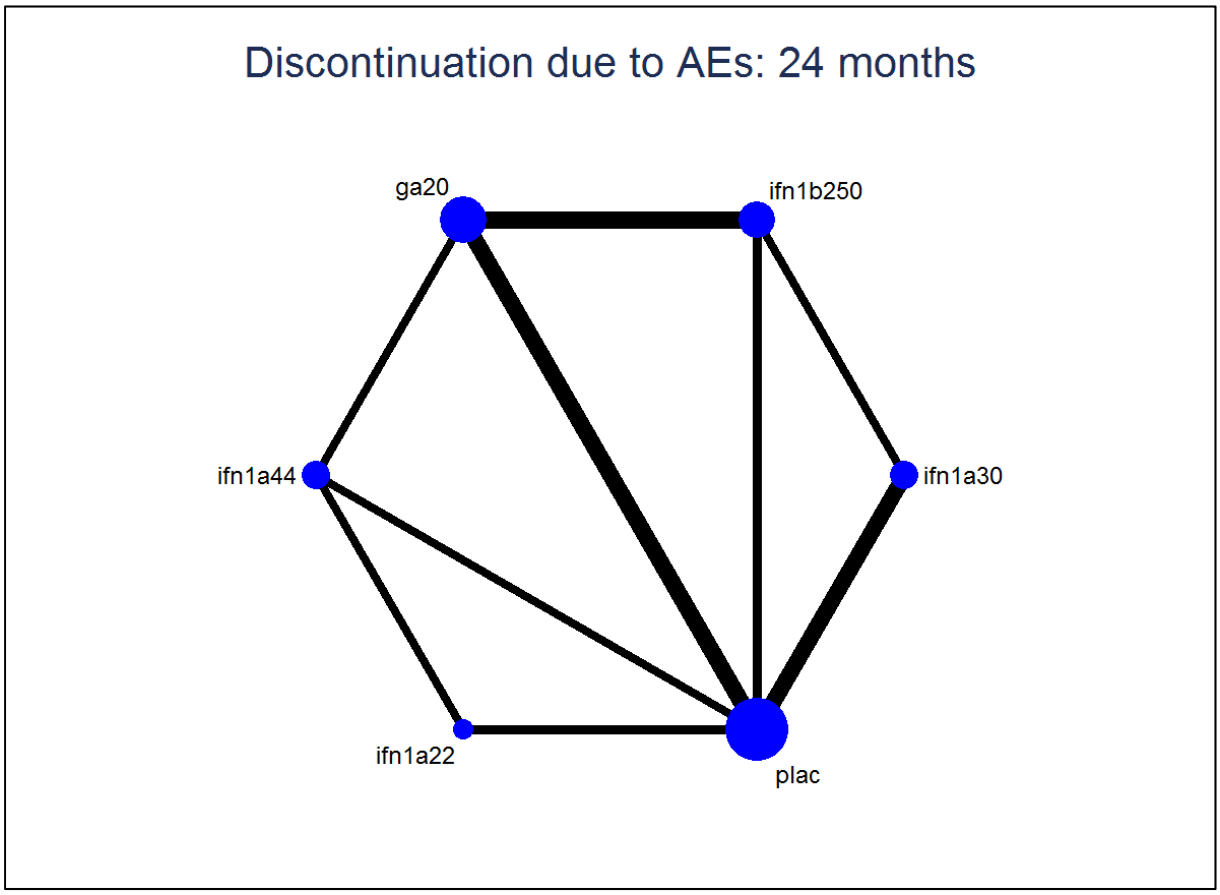


Table 13: Network meta-analysis: Discontinuation due to AEs at 24 months in RRMS

Findings are presented as risk ratios with 95% CI.

Drug	**SUCRA**	**IFN β-1b 250 µg SC every other day**	**IFN β-1a 44 µg SC thrice weekly**	**GA 20 mg daily**	**IFN β-1a 22 µg SC thrice weekly**	**IFN β-1a 30 µg IM weekly**	**Placebo**
IFN β-1b 250 µg SC every other day	0.79		1.15 (0.20, 6.56)	1.70 (0.50, 5.81)	2.37 (0.22, 25.84)	2.74 (0.56, 13.38)	4.41 (1.07, 18.29)
IFN β-1a 44 µg SC thrice weekly	0.76			1.48 (0.39, 5.57)	2.07 (0.32, 13.44)	2.39 (0.38, 15.22)	3.85 (0.81, 18.29)
GA 20 mg daily	0.57				1.40 (0.17, 11.76)	1.61 (0.38, 6.91)	2.60 (0.88, 7.64)
IFN β-1a 22 µg SC thrice weekly	0.41					1.15 (0.10, 13.09)	1.86 (0.21, 16.83)
IFN β-1a 30 µg IM weekly	0.35						1.61 (0.52, 5.02)
Placebo	0.12						
Wald test for inconsistency (χ2, df, p)	2.38, 3, 0.50						

In comparison with the direct evidence from IFNB MSSG 1995,[208] estimates for discontinuation due to AEs in IFN β-1b 250 μg SC every other day against placebo were lower but remained statistically significant (risk ratio=4.41, 95% CI [1.07, 18.29]). Estimates for IFN β-1a 44 μg SC thrice weekly were lower in the NMA (3.85, [0.81, 18.29]) than in pairwise estimate derived from PRISMS 1998[187] (7.11, [0.88, 57.25]), as were estimates for IFN β-1a 22 μg SC thrice weekly (NMA: 1.86, [0.21, 16.83] vs. PRISMS 1998: 2.97 [0.31, 28.28]). However, estimates for GA 20 mg SC once daily as compared to placebo were higher in the NMA (2.60, [0.88, 7.64]) as compared to the pairwise meta-analysis (1.69, [0.51, 5.58]).

An overall test for inconsistency across the network did not suggest the presence of inconsistency (p=0.50). However, a side-splitting test did find that direct and indirect evidence were in conflict for the comparison between GA 20 mg SC once daily and placebo, with indirect evidence suggesting that risk of discontinuation due to AEs was higher than presented in the direct evidence (p=0.037). Thus, there is some evidence of inconsistency in this network.

Discontinuation due to adverse events: all follow-up times

Pairwise meta-analyses

Pairwise meta-analyses for discontinuation due to AEs across all time points are shown in Figure 19. There was no visual evidence of a systematic difference based on the strict definition of the outcome. In every pairwise meta-analysis, confidence intervals were wide, as would be expected. Five pooled estimates relied on multiple studies: GA 20 mg SC once daily vs. placebo, IFN β-1a 30 μg IM once a week vs. placebo, and IFN β-1b 250 μg SC every other day vs. each of placebo, GA 20 mg SC once daily, and IFN β-1a 44 μg SC thrice weekly.

Despite visual evidence suggesting that discontinuation due to AEs was more likely in study arms testing active drugs as compared to study arms testing placebo, almost all individual study estimates and pooled estimates did not suggest that discontinuation was more likely in trial arms corresponding to one drug over another to a statistically significant level,. The one exception was IFN β-1a pegylated 125 μg every two weeks as compared to placebo, in which patients receiving the study drug were more likely to discontinue the study due to AEs (risk ratio=3.49, 95% CI [1.52, 7.99]). Estimates for GA 40 mg SC three times weekly were marginally non-significant (2.36, [0.99, 5.65]). Again, both estimates relied on one study. Of note is that comparisons between GA 20 mg SC once daily and placebo, which included five studies, did not suggest a substantial relationship between the study drug and discontinuation (1.07, [0.64, 1.79]), but this was driven (at least in part) by the null finding from CONFIRM 2012[214] (0.95 [0.62, 1.47]).

Network meta-analysis

The studies included in this analysis formed a connected network (see Figure 20). All drugs were compared to placebo, and all drugs were included in this analysis.

The NMA, which was estimated with random effects per the protocol, generated estimates of each drug against placebo and against every other drug (see Table 14). The NMA did not offer statistical evidence that any one drug was more likely to result in discontinuation due to AEs as compared to another. Based on SUCRAs, IFN

β-1a pegylated 125 μg every two weeks was ranked highest on risk of discontinuation due to AEs (i.e. greatest risk of discontinuation), followed by IFN β-1a 44 μg SC thrice weekly. Placebo was ranked last.

Because confidence intervals were frequently wide in pairwise, direct meta-analyses, confidence intervals were wide in the NMAs and estimates as compared to placebo were often numerically different. Compared with direct estimates from PRISMS 1998,[187] evidence from the NMA suggested a numerically lower risk of discontinuation due to AEs in IFN β-1a 44 μg SC thrice weekly as compared to placebo (NMA: risk ratio=2.49, 95% CI [0.89, 6.95]; PRISMS 1998: 7.11, [0.88, 57.25]). That is, the magnitude of the risk of discontinuation as compared to placebo was smaller in the NMA than in the one trial informing the direct comparison. The same applied for IFN β-1a 22 μg SC thrice weekly (NMA: 1.24, [0.21, 7.26]; PRISMS 1998: 2.97, [0.31, 28.28]). Similarly, estimates for discontinuation due to AEs in IFN β-1b 250 μg SC every other day vs. placebo were lower in the NMA than in the pairwise meta-analysis (NMA: 1.75, [0.63, 4.89]; pairwise meta-analysis: 4.93, [0.76, 32.00]). Estimates of discontinuation due to AEs were higher in the NMA for GA 20 mg SC once daily vs. placebo (NMA: 1.56, [0.77, 3.14]; pairwise meta-analysis: 1.07, [0.64, 1.79]).

An overall Wald test for inconsistency in the network did not reach significance, but suggested some conflict between direct and indirect evidence (p=0.09). Examination of the specific design effects from the design-by-treatment interaction model suggested that direct estimates of discontinuation due to AEs from IFN β-1b 250 μg SC every other day vs. placebo could be driving this result (design effect p=0.075). However, a side-splitting test did not suggest an obvious source of conflict between direct and indirect evidence. Thus, while there is no statistically significant evidence of inconsistency in this network, findings should be viewed with caution.

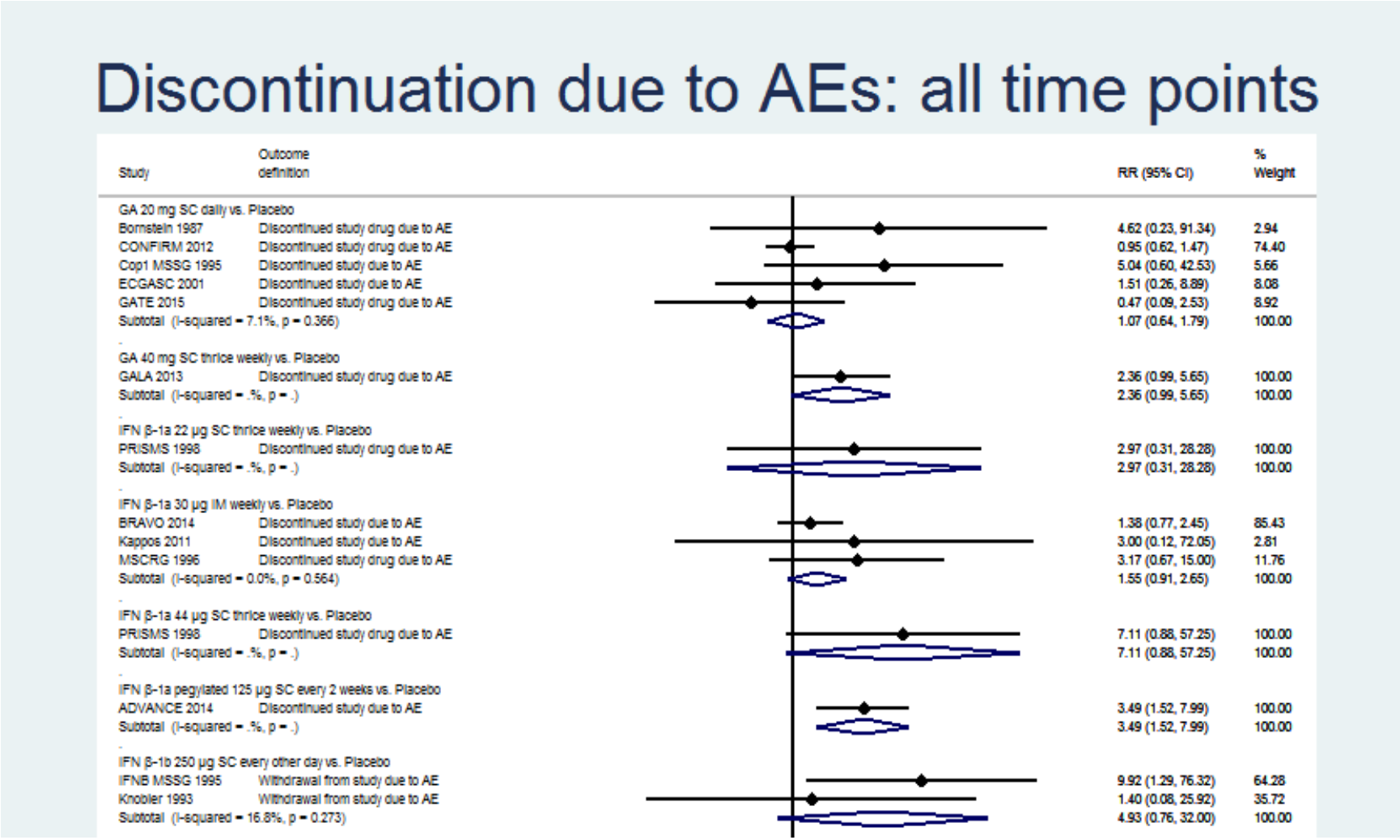
Comparison of network meta-analyses: modal follow-up vs. all time points

Neither NMA found evidence that one drug was superior to another.

However, estimates for discontinuation due to AEs for active drugs against placebo tended to be lower in the network including all time points, possibly since the majority of studies included in this analysis that were set aside in the modal follow-up analysis included shorter follow-up periods (generally of one year or shorter). Estimates were essentially unchanged for IFN β-1a 30 μg IM once a week vs. placebo (modal follow-up: risk ratio=1.61, 95% CI [0.52, 5.02]; all time points: 1.62, [0.82, 3.23]).

Figure 19: Pairwise meta-analyses: discontinuation due to AEs at all time points in RRMS

In this plot, RR=risk ratio.



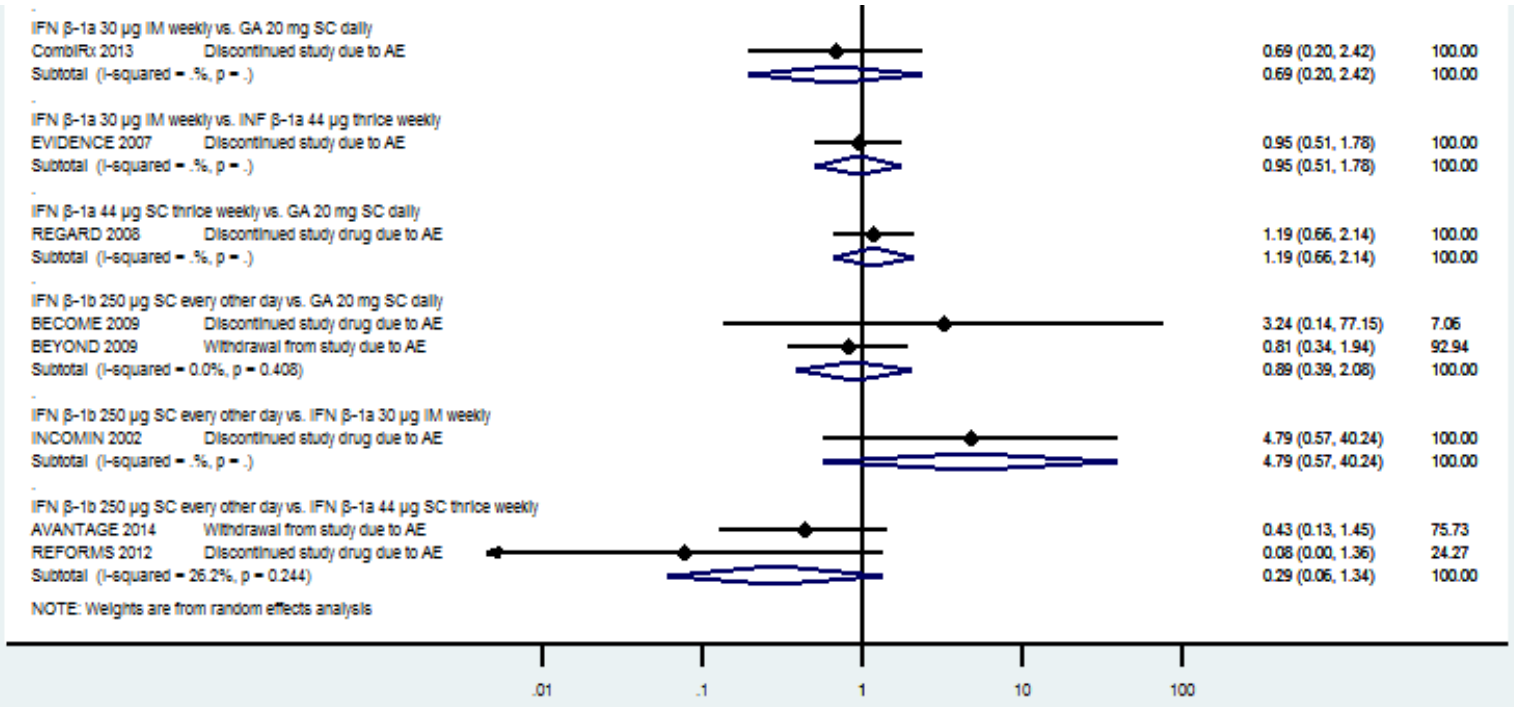

IFN β-1a 30 µg IM weekly vs. GA 20 mg SC daily
CombiRx 2013 Discontinued study due to AE 0.69 (0.20, 2.42) 100.00
Subtotal (I-squared = .%, p = .) 0.69 (0.20, 2.42) 100.00
IFN β-1a 30 µg IM weekly vs. INF β-1a 44 µg thrice weekly
EVIDENCE 2007 Discontinued study due to AE 0.95 (0.51, 1.78) 100.00
Subtotal (I-squared = .%, p = .) 0.95 (0.51, 1.78) 100.00
IFN β-1a 44 µg SC thrice weekly vs. GA 20 mg SC daily
REGARD 2008 Discontinued study drug due to AE 1.19 (0.66, 2.14) 100.00
Subtotal (I-squared = .%, p = .) 1.19 (0.66, 2.14) 100.00
IFN β-1b 250 µg SC every other day vs. GA 20 mg SC daily
BECOME 2009 Discontinued study drug due to AE 3.24 (0.14, 77.15) 7.06
BEYOND 2009 Withdrawal from study due to AE 0.81 (0.34, 1.94) 92.94
Subtotal (I-squared = 0.0%, p = 0.408) 0.89 (0.39, 2.08) 100.00
IFN β-1b 250 µg SC every other day vs. IFN β-1a 30 µg IM weekly
INCOMIN 2002 Discontinued study drug due to AE 4.79 (0.57, 40.24) 100.00
Subtotal (I-squared = .%, p = .) 4.79 (0.57, 40.24) 100.00
IFN β-1b 250 µg SC every other day vs. IFN β-1a 44 µg SC thrice weekly
AVANTAGE 2014 Withdrawal from study due to AE 0.43 (0.13, 1.45) 75.73
REFORMS 2012 Discontinued study drug due to AE 0.08 (0.00, 1.36) 24.27
Subtotal (I-squared = 26.2%, p = 0.244) 0.29 (0.06, 1.34) 100.00
NOTE: Weights are from random effects analysis
.01
.1
1
10
100

Figure 20: Network of studies, discontinuation due to AEs at all time points in RRMS

ifn1a30: IFN β-1a 30 µg IM once a week; ifn1a44: IFN β-1a 44 µg SC three times weekly; ifn1a22: IFN β-1a 22 µg SC three times weekly; ifn1b250: IFN β-1b 250 µg SC every other day; peg: IFN β-1a pegylated 125 µg SC every two weeks; ga20: GA 20 mg SC once daily; ga40: GA 40 mg SC thrice weekly; plac: placebo

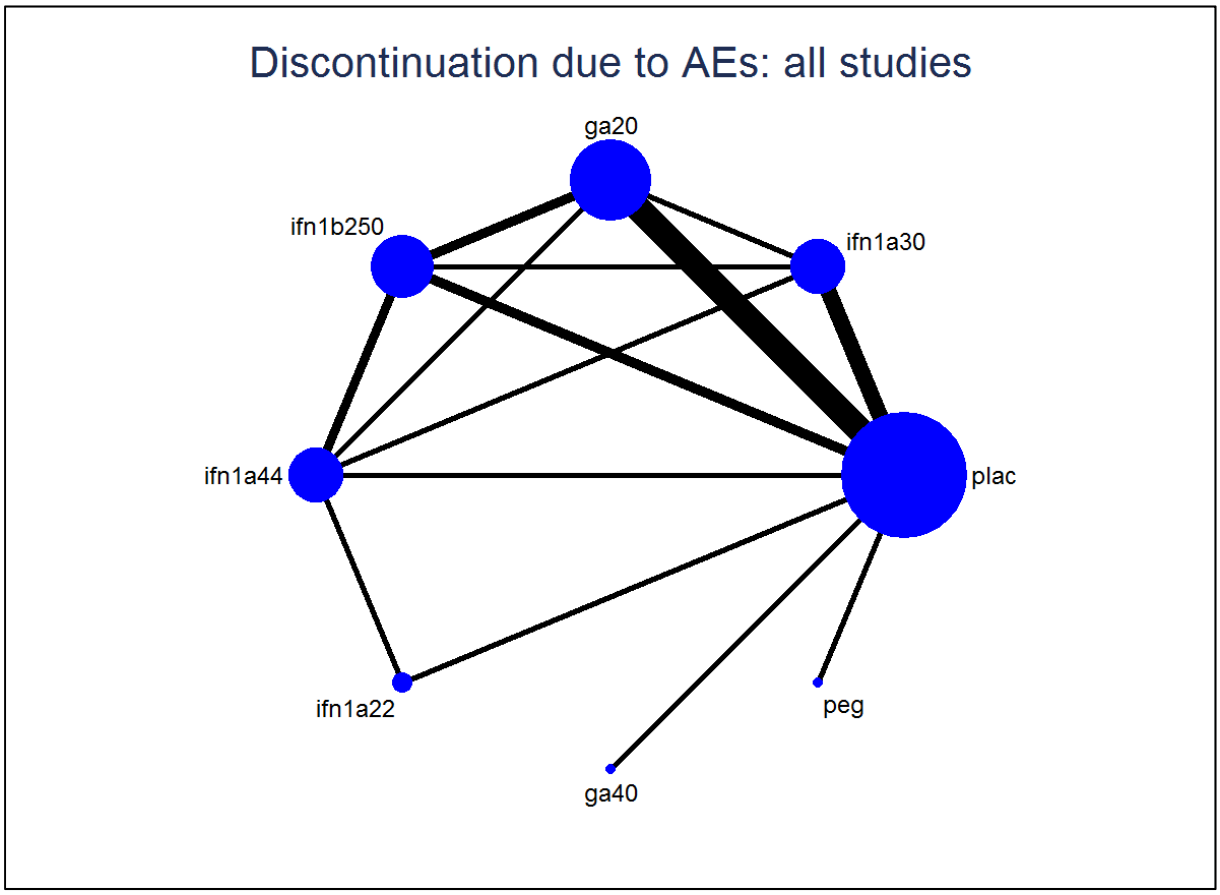


Table 14: Network meta-analysis: Discontinuation due to AEs at all time points in RRMS

Findings are presened as risk ratios with 95% CI.

Drug	SUCRA	IFN β-1a pegylated 125 µg every 2 weeks	IFN β-1a 44 µg SC thrice weekly	GA 40 mg thrice weekly	IFN β-1b 250 µg SC every other day	IFN β-1a 30 µg IM weekly	Glatiramer 20 mg daily	IFN β-1a 22 µg SC thrice weekly	Placebo
IFN β-1a pegylated 125 µg every 2 weeks	0.82		1.40 (0.31, 6.45)	1.48 (0.29, 7.43)	1.99 (0.43, 9.15)	2.15 (0.57, 8.04)	2.24 (0.59, 8.44)	2.82 (0.35, 23.04)	3.49 (1.13, 10.76)
IFN β-1a 44 µg SC thrice weekly	0.73			1.05 (0.22, 4.95)	1.42 (0.61, 3.30)	1.53 (0.65, 3.59)	1.60 (0.76, 3.36)	2.01 (0.45, 9.01)	2.49 (0.89, 6.95)
Glatiramer 40 mg thrice weekly	0.66				1.35 (0.29, 6.35)	1.45 (0.38, 5.60)	1.52 (0.39, 5.89)	1.91 (0.23, 15.88)	2.36 (0.74, 7.53)
IFN β-1b 250 µg SC every other day	0.50					1.08 (0.42, 2.79)	1.12 (0.51, 2.49)	1.42 (0.26, 7.71)	1.75 (0.63, 4.89)
IFN β-1a 30 µg IM weekly	0.45						1.04 (0.51, 2.13)	1.32 (0.24, 7.17)	1.62 (0.82, 3.23)
Glatiramer 20 mg daily	0.40							1.26 (0.24, 6.50)	1.56 (0.77, 3.14)
IFN β-1a 22 µg SC thrice weekly	0.33								1.24 (0.21, 7.26)
Placebo	0.12								
Wald test for inconsistency (χ2, df, p)	11.04, 6, 0.09								

9.5.18 Summary: relapsing remitting MS

Across drugs, studies suggested and meta-analyses confirmed that interferons and GA reduce relapse rate, reduce rate of severe relapses (both as measured by neurological rating scales and as measured by steroid treatment), and generally delay disability progression. However, findings were clearer for disability progression confirmed at 3 months as opposed to confirmed at 6 months. There was little evidence that any one drug was superior to others except for disability progression confirmed at 6 months, but networks were especially sparse. Findings for progression confirmed at 3 months did not match results from progression confirmed at 6 months. Findings for freedom from disease activity, MS symptoms and health-related quality of life were infrequently reported, and evidence for MS symptoms and health-related quality of life also suffered from poor reporting. Findings for discontinuations due to AEs, which are intended to be indicative, did not suggest that one drug was more likely to result in discontinuation than another, or, with few exceptions, against placebo. However, findings for discontinuation relied on networks with some limited evidence of inconsistency.

9.6 *Clinical effectiveness: secondary progressive MS*

Our analysis was informed by three included trials: European Study Group on Interferon β-1b in Secondary Progressive MS 1998 (referred to as ESG 1998[220]), North American Study Group on Interferon beta-1b in Secondary Progressive MS 2004 (referred to as NASG 2004[221]) and SPECTRIMS 2001.[222] It should be noted that while all studies included both relapsing and non-relapsing patients, only SPECTRIMS 2001 presented subgroup analyses by history of previous relapses in SPMS.

9.6.1 IFN β-1a 44 µg and 22 µg SC three times a week (Rebif) vs. placebo

One trial evaluated both 44 µg and 22 µg doses of IFN β-1a against placebo: SPECTRIMS 2001.[222]

Relapse outcomes

In SPECTRIMS 2001,[222] 618 patients were followed up for three years. Rate ratios (RaR) based on annualised relapse rates (ARRs) were numerically identical for both active arms as compared to placebo (44 µg: RaR=0.69, 95% CI [0.56, 0.85]; 22 µg: RaR=0.69, 95% CI [0.56, 0.84]).

Subgroup analyses stratifying by whether patients had history of relapse showed a pattern of significant results for those previously relapsing and non-significant results for those not previously relapsing.[222] For those previously relapsing, ARRs were significantly different from the placebo arm (1.08) in the 44 µg dose (0.67, $p<0.001$) and the 22 µg dose (0.57, $p<0.001$). For those not previously relapsing, ARRs were not significantly different from the placebo arm (0.39) in either dosage (44 µg: 0.43, $p>0.05$; 22 µg: 0.36, ns).

Both active arms also had similar delays in time to first relapse, though only the 44 µg dose had a significant effect against placebo (HR 0.77, 95% CI [0.61, 0.98]), corresponding to a difference in median time to first relapse of 494 days vs. 281 days.[222] Though the difference in median time to relapse of the 22 µg dose was similar (476 days vs. 281 days), this did not translate into a significant effect (HR=0.87, [0.69, 1.10]). The

difference between the two active arms was not calculated in this trial, though an approximation is that the HR of 44 µg vs 22 µg would be (0.77÷0.87)=0.89 and not statistically different from unity.

Relapse severity

Both arms showed similar reductions in the annualised rates of moderate or severe relapses (44 µg: RaR=0.68, 95% CI [0.44, 0.81]; 22 µg: 0.66, 95% CI [0.51, 0.86]).[222] Findings were similar for annualised rates of steroid courses used to treat relapses (44 µg: 0.66, 95% CI [0.49, 0.89]; 22 µg: 0.59, [0.44, 0.81]).

Disability progression

In SPECTRIMS 2001, disability progression was confirmed at 3 months.[222] Neither active drug arm was associated with a significant decrease in hazard for time to confirmed disability progression in the main analysis (44 µg: HR=0.83, 95% CI [0.65, 1.07]; 22 µg: 0.88, *p*=0.305), nor were active arms substantially different. However, an analysis controlling for disease characteristics found a significant difference in the 44 µg arm (0.78, [0.60, 1.00]).

Subgroup analyses combined the two dosages into one arm and stratified models by whether patients had history of relapse.[222] The hazard ratio for time to confirmed disability progression suggested a positive, though non-significant, effect in previously relapsing patients (0.74, *p*=0.055), while the hazard ratio approached unity in non-relapsing patients (1,01, *p*=0.934). However, amongst previously relapsing patients, *proportions* of patients with confirmed disability progression were significantly different between those receiving 44/22 µg and those receiving placebo (OR=0.52, 95% CI [0.29, 0.93]), but not amongst those not previously relapsing (OR=1.07, 95% CI [0.64, 1.78]).

Freedom from disease activity

We were unable to locate any relevant comparisons between IFN β-1a 44 µg or 22 µg SC three times a week and combined clinical-MRI outcomes for freedom from disease activity.

MS symptoms and health-related quality of life

We were unable to locate any relevant comparisons between IFN β-1a 44 µg or 22 µg SC three times a week and placebo for MS symptoms and health-related quality of life.

Adverse events and mortality

SPECTRIMS 2001[222] reported AEs and mortality. Full results are available on request. Differences on mortality were not significantly different between groups; one patient died in the placebo arm of SPECTRIMS 2001 whereas two patients died in the 44 µg arm and one patient died in the 22 µg arm.

9.6.2 IFN β-1b 250 µg SC every other day (Betaferon/Extavia) vs. placebo

Two trials evaluated IFN β-1b 250 µg SC every other day: ESG 1998[220, 223] and NASG 2004.[221] NASG 2004 included a dosing arm of IFN β-1b that is not recommended and thus not included in this analysis.

Relapse outcomes

In ESG 1998,[220, 223] 718 patients were followed for up to two years. Patients receiving the study drug had a significantly lower ARR (0.42) than those in the placebo arm (0.42 vs. 0.57, p=0.003). We approximated this as a rate ratio of 0.74 (95% CI 0.65, 0.83). Similarly, for the 623 patients enrolled in the relevant study arms in NASG 2004[221] and followed for up to three years before early study termination, patients receiving the study drug had a significantly lower ARR than placebo patients (0.16 vs. 0.28, p=0.009). We estimated this as corresponding to a rate ratio of 0.57 (0.43, 0.75).

Both studies also demonstrated statistically significant delays in time to first relapse. In interim data from ESG 1998,[220] median time to first relapse was 644 days in the study drug arm vs. 403 days in the placebo arm (log rank p=0.003). In NASG 2004,[221] end-of-study data demonstrated a time to relapse at the 30th percentile of 1051 days in the study drug arm vs. 487 days in the placebo arm (log rank p=0.01). However, proportions relapsing were not significantly different in ESG 1998[220] (57.5% in the study drug arm vs. 62.0% in placebo, p=0.083), though NASG 2004 did yield a significant difference (29% vs. 38%, p=0.018).

Relapse severity

Both studies showed significant differences between study drug and placebo in proportions of patients experiencing moderate or severe relapses (ESG 1998[220] interim data: 43.6% vs. 53.1%, p=0.0083; NASG 2004:[221] 21% vs. 30%, p=0.012). In NASG 2004, the annualised rate of moderate or severe relapses was significantly less in the study drug arm than in the placebo arm (0.10 vs. 0.19, p=0.022). However, it should be noted that outcome tables for NASG 2004 presented two estimates of relapse severity with markedly different results. Under the second set of estimates, neither proportion of patients with moderate or severe relapses (3% vs. 6%, p=0.056) or annualised rate of moderate or severe relapses (0.01 vs. 0.02, p=0.052) were significantly different between arms. Contact with study investigators did not yield clarification.

In both studies, the percentage of patients treated with steroids also decreased significantly (ESG 1998[220] interim data: 53.6% vs. 67.9%, p<0.0001; NASG 2004:[221] 37% vs. 46%, p=0.023).

Disability progression

In the final results of ESG 1998,[223] progression was measured using a variety of criteria, including progression of at least 1.0 EDSS points confirmed at 3 months and confirmed at 6 months, and progression of 2.0 EDSS points confirmed at 3 months. Each of these measures was estimated both excluding data collected during relapses (the default) and including relapse data, but proportions were similar in all cases between measures including and excluding data collected during relapses; thus we discuss only the default measures here. The proportion of patients progressing at least 1.0 EDSS point confirmed at three months was significantly less in the study drug arm than in the placebo arm (45.3% vs. 53.9%, p=0.031). Combined with estimated probabilities from a life table model (estimated non-progression at 33 months 53% vs. 44%) and a log rank p-value of 0.003, this yielded an approximate HR of 0.75 (95% CI [0.61, 0.92]). Proportions with confirmed progression at 6 months (40.8% vs. 48.6%, p=0.049) and with confirmed progression of at least 2.0 EDSS points at 3 months

(16.4% vs. 22.6%, *p*=0.032) showed similar trends. However, in NASG 2004,[221] disability progression was confirmed at 6 months and did not show a significant difference in terms of time to progression (study drug 32% vs. placebo 34%, log rank *p*=0.61).

Similarly, while patients in ESG 1998[223] did show significant differences in average points of EDSS progression between arms (0.47 vs. 0.69, *p*=0.003), patients in NASG 2004[221] did not (0.53 vs. 0.62, *p*=0.634).

Freedom from disease activity

We were unable to locate any relevant comparisons between IFN β-1b 250 μg SC every other day and combined clinical-MRI outcomes for freedom from disease activity.

MS symptoms and health-related quality of life

In NASG 2004,[221] change from baseline was not significantly different between patients in the study drug arm and patients in the placebo arm on fatigue (Environmental Status Scale change 1.7 vs. 1.2, *p*=0.125), cognition (composite neuropsychological score -0.28 vs. -0.32, *p*=0.42) or depression (Beck Depression Inventory score -0.5 vs. -1.0, *p*=0.652; percentage newly treated with antidepressants 29% vs. 29%, *p*=0.987). Changes in overall Multiple Sclerosis Quality of Life Inventory scores were not significantly different either (*p*=0.502).

Adverse events and mortality

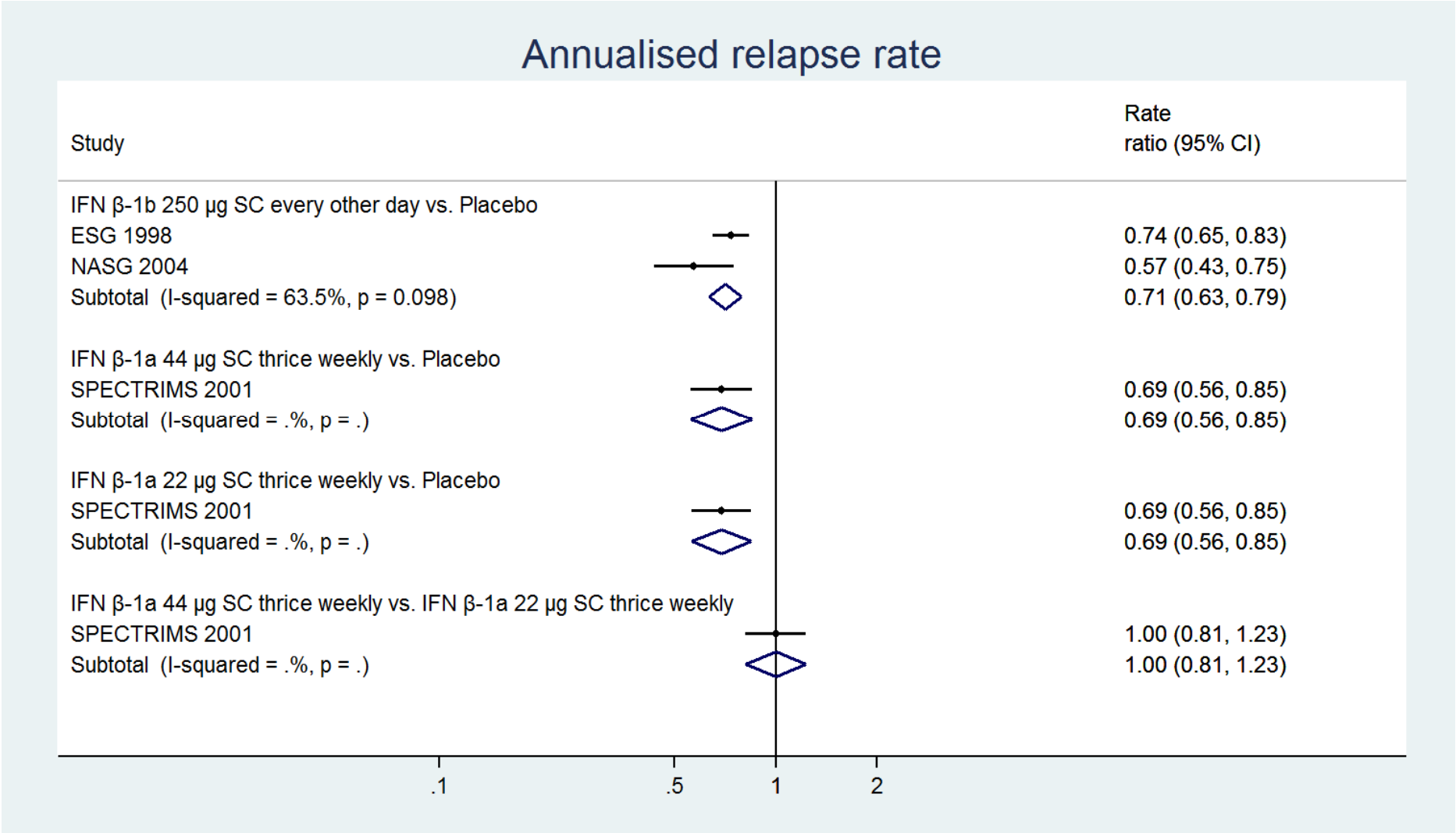
Both studies reported AEs and mortality. Full results are available on request. Studies were not significantly different on mortality, though there were a combined seven deaths in the IFN β-1b 250 μg SC every other day arms and a combined two deaths in the placebo arms of the two trials.

9.6.3 Meta-analyses: relapse rate

Pairwise meta-analyses

Direct evidence from comparisons is shown in Figure 21. Aside from SPECTRIMS 2001,[222] which compared IFN β-1a 44 μg SC thrice weekly, IFN β-1a 22 μg SC thrice weekly and placebo, the other two included studies compared IFN β-1b 250 μg SC every other day against placebo. The pooled effect of IFN β-1b 250 μg SC every other day against placebo suggested that the drug reduces the rate of relapse (RR=0.71, 95% CI [0.63, 0.79]).

Figure 21: Pairwise meta-analyses: ARR in SPMS



Network meta-analysis

Ranking of drugs in the resultant network suggested that IFN β-1b 250 µg SC every other day was superior to the equally ranked IFN β-1a 44 µg SC thrice weekly and IFN β-1a 22 µg SC thrice weekly (see Table 15). Placebo was ranked last. Findings for comparisons between active drugs and placebo were, as would be expected, essentially the same as in the direct evidence. Comparisons between IFN β-1b 250 µg SC every other day and both IFN β-1a 44 µg SC thrice weekly and IFN β-1a 22 µg SC thrice weekly did not suggest a statistical difference between the drugs in effectiveness (44 µg: HR=0.97, 95% CI [0.63, 1.50]; 22 µg: HR=0.97, 95% CI [0.63, 1.49]).

Because there was not the possibility for inconsistency in the network, we did not test for it.

Table 15: Network meta-analysis: annualised relapse rates in SPMS

Drug	SUCRA	IFN β-1b 250 µg SC every other day	IFN β-1a 44 µg SC thrice weekly	IFN β-1a 22 µg SC thrice weekly	Placebo
IFN β-1b 250 µg SC every other day	0.71		0.97 (0.63, 1.50)	0.97 (0.63, 1.49)	0.67 (0.52, 0.86)
IFN β-1a 44 µg SC thrice weekly	0.64			1.00 (0.71, 1.42)	0.69 (0.49, 0.98)
IFN β-1a 22 µg SC thrice weekly	0.64				0.69 (0.49, 0.98)
Placebo	0.01				

9.6.4 Meta-analyses: relapse severity

We did not undertake meta-analyses for relapse severity in SPMS because of the quality and scarcity of the data.

9.6.5 Meta-analyses: time to disability progression confirmed at three months

Pairwise meta-analyses

Direct evidence from comparisons is shown in Figure 22. Comparisons included two trials: SPECTRIMS 2001[222] and ESG 1998.[220, 223] Findings are the same as for the individual trials.

Network meta-analysis

Because of the shape of the network, in which there was no opportunity for inconsistency and in which no direct comparison was informed by more than one trial, the model was estimated using fixed effects instead of random effects as in the protocol. Ranking of drugs in the resultant network suggested that IFN β-1b 250 µg SC every other day was superior to IFN β-1a 44 µg SC thrice weekly and to IFN β-1a 22 µg SC thrice weekly (see Table 16). Placebo was ranked last. Findings for comparisons between active drugs and placebo were, as would be expected, essentially the same as in the direct evidence. Comparisons between IFN β-1b 250 µg SC every other day and both IFN β-1a 44 µg SC thrice weekly and IFN β-1a 22 µg SC thrice weekly did not suggest a statistical difference between the drugs in effectiveness (44 µg: HR=0.91, 95% CI [0.65, 1.25]; 22 µg: HR=0.85, 95% CI [0.62, 1.18]). Because there was no possibility for inconsistency in the network, we did not test for it.

Figure 22: Pairwise comparisons: time to disability progression confirmed at 3 months in SPMS

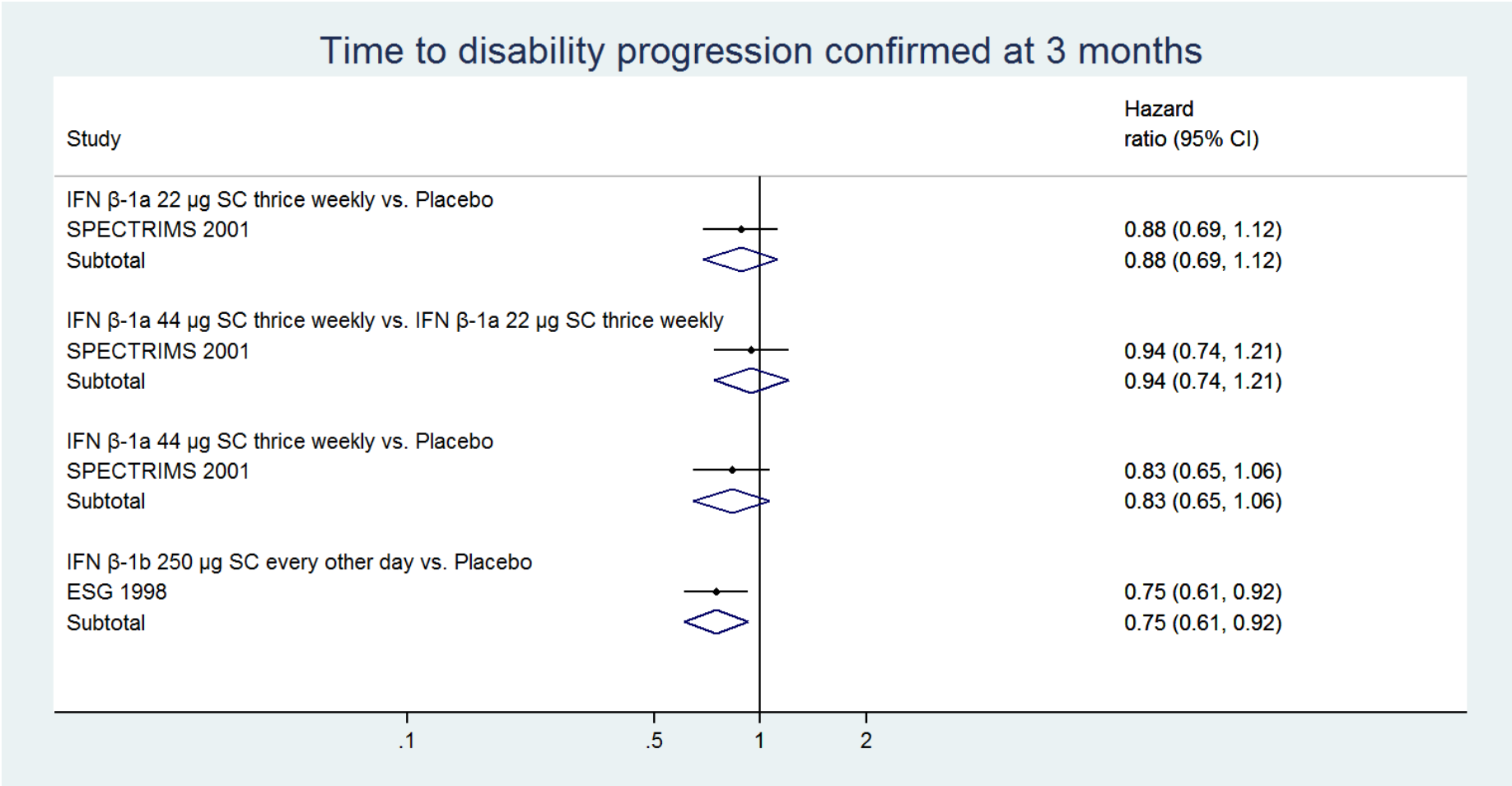


Table 16: Network meta-analysis: time to disability progression confirmed at 3 months in SPMS

Drug	SUCRA	IFN β-1b 250 µg SC every other day	IFN β-1a 44 µg SC thrice weekly	IFN β-1a 22 µg SC thrice weekly	Placebo
IFN β-1b 250 µg SC every other day	0.85		0.91 (0.65, 1.25)	0.85 (0.62, 1.18)	0.75 (0.61, 0.92)
IFN β-1a 44 µg SC thrice weekly	0.64			0.94 (0.74, 1.21)	0.83 (0.65, 1.06)
IFN β-1a 22 µg SC thrice weekly	0.44				0.88 (0.69, 1.12)
Placebo	0.07				

9.6.6 Meta-analyses: time to disability progression confirmed at six months

Only one study, NASG 2004,[221] reported an effect size for time to disability progression confirmed at six months. In their comparison of IFN β-1b 250 µg SC every other day and placebo, they did not find a statistically significant effect on time to disability progression. We imputed this hazard ratio as 0.93 (95% CI [0.71, 1.22]).

9.6.7 Meta-analyses: adverse events

Summary of adverse events meta-analyses

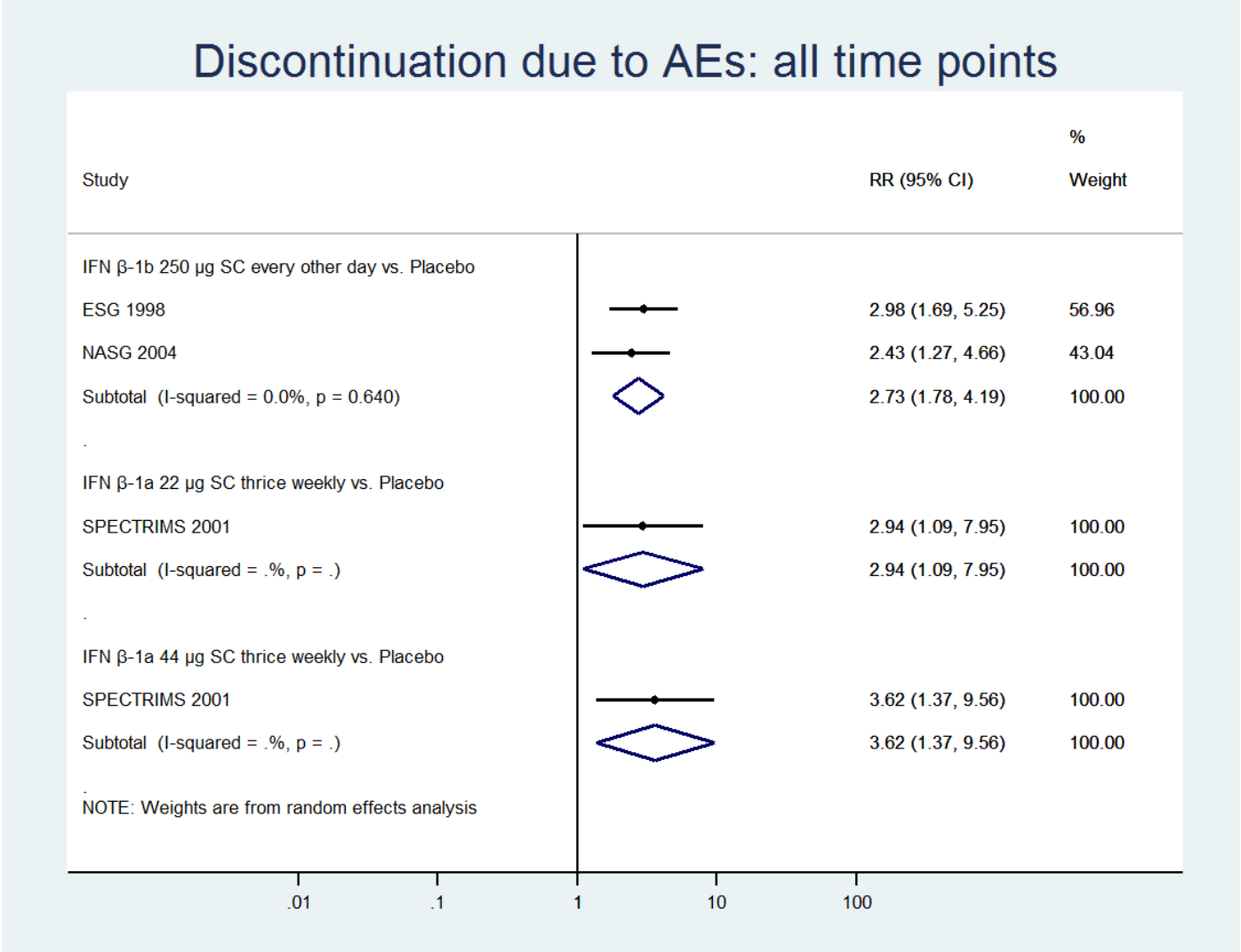
Full results for pairwise meta-analyses of AEs are available on request. Though the diversity and heterogeneity of AEs precludes detailed examination of each, several trends were apparent across pairwise comparisons. Comparing IFN β-1a SC thrice weekly vs. placebo, IFN β-1a was associated with more application site disorders, necrosis, increased alanine aminotransferase (SGPT), increased aspartate aminotransferase (SGOT), leucopenia, lymphopenia, neutralising antibodies and the numbers of patients who discontinued study treatment due to AE. Comparing IFN β-1b 250 µg SC every other day vs. placebo, IFN β1b was associated with more injection site inflammation, necrosis, pain, injection site reaction, chest pain, chills only, chills and fever, fever only, flu syndrome, hypertonia, leucopenia, lymphadenopathy, lymphopenia, neutralising antibodies, rash and the number of patients who discontinued study treatment due to AE.

Meta-analyses: discontinuation due to adverse events

Pairwise meta-analyses

All three studies presented data for discontinuation of the study drug due to AEs, and all studies included follow-up of 36 months. Pairwise estimates are in Figure 23. As compared to placebo, all drugs were associated with a significant increase in risk of discontinuation of the study drug due to AEs.

Figure 23: Pairwise meta-analyses: discontinuation due to AEs in SPMS



Network meta-analysis

Studies formed a star-shaped network. Examination of SUCRAs in the resultant network suggested that IFN β-1a 44 µg SC thrice weekly was ranked highest (i.e. associated with the greatest risk) for discontinuation of the study drug due to AEs, followed by IFN β-1a 22 µg SC thrice weekly and then IFN β-1b 250 µg SC every other day (see Table 17). Placebo was ranked last.

As would be expected, estimates from comparisons with placebo were unchanged in the NMA as compared to the pairwise meta-analysis. There was no evidence from the NMA that one drug was more likely to result in discontinuations due to AEs than any other drug.

Because there was no opportunity for inconsistency in the network, we did not test for it.

Table 17: Network meta-analysis: Discontinuation due to AEs in SPMS

Drug	SUCRA	IFN β-1a 44 µg SC thrice weekly	IFN β-1a 22 µg SC thrice weekly	IFN β-1b 250 µg SC every other day	Placebo
IFN β-1a 44 µg SC thrice weekly	0.81		1.23 (0.64, 2.37)	1.32 (0.46, 3.83)	3.62 (1.37, 9.56)
IFN β-1a 22 µg SC thrice weekly	0.60			1.08 (0.37, 3.18)	2.94 (1.09, 7.95)
IFN β-1b 250 µg SC every other day	0.58				2.73 (1.78, 4.19)
Placebo	0.01				

9.6.8 Summary: secondary progressive multiple sclerosis

Studies did not consistently report findings for SPMS patients with recent history of relapses. Thus, findings should be regarded with caution. Taken together, the three studies suggested that the included drugs reduced relapse rate and relapse severity relative to placebo, though we were unable to clarify issues with relapse severity data from one trial. Findings for disability progression were mixed. We were unable to locate any relevant comparisons on combined clinical-MRI measures of freedom from disease activity. One study reported MS symptom data and did not find evidence of differences between the study drug and placebo. There were no significant differences between study drugs and placebo on mortality. Each drug was associated with increased risk of discontinuation due to AEs.

NMAs for ARR and time to disability progression confirmed at three months did not suggest superiority of one drug over another, nor did NMAs for discontinuation due to AEs suggest that one drug was more likely to result in discontinuation over another. We did not undertake meta-analyses for relapse severity due to unresolved questions about one of the three included studies, and only one included study reported time to disability progression confirmed at six months.

9.7 *Overall summary of clinical effectiveness findings*

In clinically isolated syndrome, each included drug showed evidence of delaying time to clinically definite MS. The NMA did not show evidence of superiority of one drug over another, though the network was sparse and only one drug was represented by more than one trial. In RRMS, drugs showed good evidence of reducing relapse rate, including rate of moderate or severe relapses and in most cases, rate of steroid-treated relapses. There was little evidence of superiority of one drug over another in reducing relapse rate. Some drugs, but not all, delayed time to disability progression confirmed at three months, though there was no evidence of superiority of one drug over any other. The network meta-analysis for time to disability progression confirmed at six months indicated that most drugs showed improvement over placebo in delaying time to progression, but this analysis was sparse and several comparisons against placebo relied solely on indirect evidence. Finally, in SPMS, all drugs reduced relapse rate, though the network was sparse and relied on three studies. Time to confirmed disability progression at three months was measured in only two studies, which showed variable effects across treatments. Analyses for discontinuation due to AEs in RRMS and SPMS were indicative, but again did not point to one drug being more likely than another to result in discontinuation due to an AE.

We were unable to undertake meta-analyses for additional outcomes—MS symptoms, health-related quality of life and freedom from disease activity—due to heterogeneity, sparsity and poor reporting for these outcomes. Additionally, no studies reported discontinuation due to loss of effect attributed to neutralising antibodies.

Conclusions are tempered by several considerations. Analyses did not show a clear 'winner' across outcomes, and, again, comparisons between drugs estimated as part of NMA models were in the main inconclusive. Though the main model for ARR was best populated, analyses for relapse severity were sparse. Analyses for time to disability progression confirmed at six months were especially sparse. In particular, several comparisons of drugs vs. placebo estimated as part of this last model relied exclusively on indirect evidence. Moreover, analyses for time to progression confirmed at three and at six months did not show a consistent pattern except that all drugs were beneficial in delaying disability progression. This is particularly concerning, as progression confirmed at six months is considered to be a 'stronger' outcome than progression confirmed at three months. NMA models also had imbalanced risk of bias across the networks of studies. For example, most active vs. active trials were open-label. Finally, trials relied on short follow-up, mostly less than two years in duration.

Looking forward, we use drug-specific estimates for ARR, for disability progression sustained at 3 months, and for disability progression sustained at 6 months as derived from our NMAs in economic modelling presented in Chapter 12. Our NMAs inform key clinical parameters in sensitivity analyses for our base case model.

10 COMPANY SUBMISSIONS: CLINICAL EFFECTIVENESS

Three submissions were received, from:

- Merck for IFN β-1a 44 µg and 22 µg IM three times weekly (Rebif),
- Teva for GA 20 mg SC daily or 40 mg SC thrice weekly (Copaxone), and
- Biogen for pegylated IFN β-1a 125 µg SC every two weeks (Plegridy) and IFN β-1a 30 µg IM weekly (Avonex).

10.1 *IFN β-1a 44 µg and 22 µg IM three times weekly (Rebif): summary of Merck submission*

The clinical effectiveness section of the submission presents an overview of the relevant trials sponsored by the manufacturer, reporting the following clinical effectiveness data.

10.1.1 Clinical effectiveness of Rebif in RRMS

The company submission stated that in patients with RRMS, Rebif demonstrated short-term and long-term efficacy in reducing relapses and delaying disease progression when compared with best supportive care. The submission included findings from PRISMS 1998,[187] including its long-term and observational extensions, to support this claim. The company submission also presented head-to-head trials, including EVIDENCE 2007,[193] IMPROVE 2012[205] and REGARD 2008.[190]

10.1.2 Clinical effectiveness of Rebif in CIS

The company submission stated that in patients with CIS, Rebif demonstrated a reduction in the number of patients who progress to a diagnosis of MS over the short and long term when compared with best supportive care. The submission included findings from REFLEX 2012,[173] including its long-term and observational extension, to support this claim.

10.1.3 Clinical effectiveness of Rebif in SPMS

The company submission stated that in trials including subsets of patients with SPMS with relapses, Rebif has some, but not significant, effect on reducing time to disability progression, and a significant effect in reducing relapse rate. The submission included findings from SPECTRIMS 2001[222] to support this claim.

10.1.4 RSS findings on clinical effectiveness of Rebif

The year 10 analysis and data for Rebif were included in the submission. The company submission stated that the hazard ratios estimated from the RSS for disability progression in Rebif as compared to best supportive care ([redacted]) were within the 10% range for the target hazard ratio needed to result in clinical effectiveness. The company submission also noted that the RSS yielded an estimate of effectiveness for Rebif similar to estimates from the PRISMS 1998 trial.

10.1.5 Our assessment of the Merck submission

Our AMSTAR assessment of the company submission can be found in Table 18.

Table 18: AMSTAR appraisal of the Merck company submission

AMSTAR Checklist	**Manufacturer's submission**
1. Was an 'a priori' design provided?	Yes - The manufacturer's submission SR protocol was described in the CS Appendix.
2. Was there duplicate study selection and data extraction?	Yes - All abstracts were reviewed by two experienced systematic reviewers according to the eligibility criteria; any difference in opinion regarding eligibility was resolved through discussion with a third reviewer. The same process was applied to the subsequent review of full papers.
3. Was a comprehensive literature search performed?	Yes - Searches were performed in the following electronic databases: MEDLINE® and MEDLINE® In-process (OVID SP); EMBASE (OVID SP); The Cochrane Central Register of Controlled Trials (CENTRAL); PubMed (for E-publications ahead of print). Abstracts from the following key international conferences were searched: Americas Committee for Treatment and Research In Multiple Sclerosis (ACTRIMS) Annual Meeting (2015); European Committee for Treatment and Research In Multiple Sclerosis (ECTRIMS) Annual Congress (2015); ACTRIMS and ECTRIMS joint meeting (2014); American Academy of Neurology (AAN) Annual Meeting (2015); American Neurological Association (ANA) Annual Meeting (2014 and 2015). Searches were run on 5 October 2015.
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	No inclusion of grey literature
5. Was a list of studies (included and excluded) provided?	Included studies were listed; excluded studies were not listed in the main submission but those excluded from the NMA were listed in the NMA document
6. Were the characteristics of the included studies provided?	Intervention, dose, regimen, N, and the data arising from the review that was used to inform the network meta-analysis are shown in the Appendix. Comparison tables of patient baseline characteristics and for the outcomes of annualised relapse rate (ARR) and sustained disability progression in the identified RCTs are available on request.
7. Was the scientific quality of the included studies assessed and documented?	Quality appraisal tables are available on request; not supplied to due volume of pages.
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Not stated that quality of studies used in formulating conclusions; no mention of sensitivity analyses by study quality.

9. Were the methods used to combine the findings of studies appropriate?	Methods appear appropriate
10. Was the likelihood of publication bias assessed?	Not stated
11. Was the conflict of interest included?	Manufacturer's submission

10.1.6 Review of network meta-analysis methods

Model type

NMA models were estimated in the Bayesian framework. Both fixed effects and random effects models were assessed according to the relative treatment-specific effect. The fit of the fixed and random effects models was compared using the deviance information criterion (DIC). Lower DIC is indicative of better fit. The best-fitting model was identified for each analysis. Where the fit was similar between fixed and random effects models, the random effects model was adopted as a conservative approach. Moreover, the NMA included a comparison of the posterior distribution of between study standard deviations with the prior distributions to assess whether it was updated by the available evidence (i.e. the additional information had had an effect). Consistency was assessed using node-splitting analyses.

[redacted]

Prior distributions and estimation

The models were fitted using the OpenBUGS software package version 3.2.2. Models used 100,000 burn-in simulations with 150,000 simulations used. Flat priors were used in all cases for the treatment-specific, study-specific and between-study variance terms.

Interventions

The NMA included all trials testing licenced drugs with dosages at or below the recommended dose. Interventions and comparators of interest were immunosuppressives or immunomodulators: alemtuzumab (Lemtrada®), BG-12 (Tecfidera®), fingolimod (Gilenya®), glatiramer acetate (Copaxone® [GA]), intramuscular IFN-β1a (Avonex®), IFN-β1b (Betaferon®), pegylated IFN-β1a, natalizumab (Tysabri), and teriflunomide (Aubagio).

Outcomes and data preparation

The NMA included analyses for ARR and disability progression. Models for disability progression included progression confirmed at 6 months with additional data from confirmation at 3 months where 6 month data were not available, and the converse; i.e. disability progression confirmed at 3 months with additional data from confirmation at 6 months where 3 month data were not available. One potential issue with this method is that

analyses are not strictly interpretable, and rely on an assumption that progression estimates from 3 months and 6 months are exchangeable, but this is unclear and may be questionable.

Authors used an optimisation algorithm to estimate person-years and number of relapses to be used with an exact Poisson likelihood. Authors also used summary hazard ratios in estimating disability progression models.

One strength of the reporting in this NMA was transparency about included effect sizes for each model.

Participants

The NMA included all patients with a diagnosis of RRMS or PRMS. The NMA included an informal assessment of similarity of baseline characteristics across trials. Authors did not undertake meta-regression or subgroup analyses.

Included trials

Unlike the assessment group's NMA, the company submission NMA included trials with comparators outside the NICE scope. However, even though the company submission NMA did not set explicit restrictions on duration of follow-up, several trials appeared to be missing from the NMA, including BRAVO 2014,[196] IMPROVE 2012,[205] Knobler 1993,[209] Kappos 2011,[197] and GATE 2015.[218] While some of these trials may have been published after the last search, it is not clear why they were excluded.

10.1.7 Findings from the network meta-analysis presented in the company submission

ARR findings

A lower ARR is indicative of better response. Though the submitted NMA covered a variety of doses and drugs, we summarise here only those results relating to licenced doses of the drugs under consideration.

[redacted]

Sustained disability progression findings

[redacted]

10.1.8 Results as compared to assessment group NMAs

For ARRs compared to placebo, the results for IFN β-1a 22 µg three times weekly and IFN β-1a 44 µg three times weekly were similar in the company's NMA and in the assessment group's NMA.

[redacted] This was also the case in the assessment group's NMA.

The 'blending' method used by the company submission NMA for analyses of sustained disability progression at 3 months and 6 months means that their analyses are not strictly commensurate with the assessment group's NMAs. Over both analyses, the assessment group's NMAs suggested a significant effect for IFN β-1a 22 µg three times weekly and IFN β-1a 44 µg three times weekly. [redacted]

10.1.9 Summary of the Merck submission

Quality of the submitted systematic review and NMA were reasonable and appropriate, and findings matched in magnitude and direction, though not always in significance, with corresponding findings from the assessment group's NMAs. The assessment group did note challenges with the interpretation of the combined disability progression models, and observed that several ostensibly relevant trials were not included in the NMA. Additionally, the company submission included trials of patients with PRMS, which was outside of the NICE scope for this submission. NMAs were not presented for CIS or SPMS.

10.2 *GA 20 mg SC daily or 40 mg SC thrice weekly (Copaxone): summary of Teva submission*

10.2.1 Clinical effectiveness of Copaxone in RRMS and CIS

The company submission states that GA in both of its doses (20 mg SC daily and 40 mg SC thrice weekly) reduces ARR and disability progression. It cites Bornstein 1987,[168] Cop1 MSSG 1995,[215] ECGASG 2001,[217] Calabrese 2012,[186] CONFIRM 2012[214] and GALA 2013[219] in support of this claim. It further notes that GA in its 20 mg SC daily dose delays progression to clinically definite MS, citing PreCISe 2009[172] and its extension.

10.2.2 RSS findings on clinical effectiveness of Copaxone

The company submission states that based on the year 10 RSS analysis, GA 20 mg SC once daily reduced EDSS disability progression at 10 years ([redacted]), with no evidence of a treatment waning effect at 10 years compared to the updated 6-year analysis. Based on the year 6 data, the company submission stated that as compared to the IFN β cohort together, the Copaxone cohort [redacted]

10.2.3 Our assessment of the Teva submission

Our assessment of the systematic review contained in the Teva submission can be found in Table 19.

Table 19: AMSTAR appraisal of the Teva company submission

AMSTAR Checklist	**Manufacturer's submission**
1. Was an 'a priori' design provided?	Yes - protocol in CS Appendix
2. Was there duplicate study selection and data extraction?	Not stated
3. Was a comprehensive literature search performed?	Yes - PubMed, Embase, Cochrane Library
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	No mention of grey literature
5. Was a list of studies (included and excluded) provided?	Included studies: yes in CS Appendix; excluded studies: no
6. Were the characteristics of the included studies provided?	Yes in CS Appendix
7. Was the scientific quality of the included studies assessed and documented?	Yes in CS Appendix
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	An analysis of the heterogeneity in the included studies was carried out and a number of potential sources of heterogeneity were identified. The main sources of heterogeneity and their impacts were investigated further through sensitivity analyses. The sensitivity analyses conducted were: exclusion of studies with less than two years follow-up, exclusion of studies with less than 50 patients *per* treatment arm, and a separate analysis was conducted of three-month and six-month confirmed disability progression. However, it does not appear that sensitivity analyses were carried out using overall quality scores. Results of RCTs were shown separately from non-randomised studies.
9. Were the methods used to combine the findings of studies appropriate?	Results tabulated but not combined in forest plots
10. Was the likelihood of publication bias assessed?	Not stated

11. Was the conflict of interest included?	Manufacturer's submission

10.2.4 Review of network meta-analysis methods

Model type

Models were estimated in the Bayesian framework. Both fixed effects and random effects models were estimated and then compared on fit. Authors also estimated pairwise meta-analyses and heterogeneity statistics.

Prior distributions and estimation

Authors used non-informative prior distributions. The authors used WinBUGS version 1.4.3 software (MRC Biostatistics Unit, Cambridge, UK) in all NMAs. In each model, two parallel chains were run, with a 50,000 iteration burn-in period. A total of 20,000 iterations against a thinning fact of 10 were sampled from each of the two chains. Convergence was assessed with Brooks-Gelman-Rubin diagnostics.

Interventions

All licenced drugs were included. Dosages were not specified, which poses significant ambiguity about whether all dosages in the literature were considered or only those which correspond to the marketing authorisation. It appears that both dosages of GA were pooled into one node in the analysis, but this was not clear.

Outcomes and data preparation

For disability progression, the authors estimated the number of events and the person-years of follow-up in each study and analysed data using a binomial likelihood with a complementary log-log link. Analyses used a model where disability progression confirmed at 6 months was preferred, with 3 months used when 6 month data were not available. Analyses of ARR used an arm-level data approach with a Poisson likelihood.

Though authors presented relevant arm-level data for trials including GA in the text of the company submission, it was not clear what the NMA inputs were. No forest plots for individual study estimates were presented.

Participants

Only participants with RRMS were included in the NMA.

Included trials

Unlike the assessment group's NMA, the company submission NMA included trials with comparators outside the NICE scope. However, authors also excluded studies with follow-up of less than 6 months. Within these restrictions, it appears that authors captured all relevant trials, though Knobler 1993[209] was not included in the analysis.

10.2.5 Findings from the network meta-analysis presented in the company submission

1.1.1.1 ARR findings

[redacted]

1.1.1.2 Sustained disability progression findings

[redacted]

10.2.6 Results as compared to assessment group NMAs

[redacted]. HRs for disability progression at 3 months and 6 months were blended and pooled across Copaxone doses in Teva's submission, but analysed separately in the assessment group NMA; thus, findings are not strictly commensurate.

[redacted] in the assessment group NMA the HR for disease progression for GA was significantly better than placebo at 3 months (0.76, [0.60, 0.97]) only, and not at 6 months (0.82, [0.53, 1.26]). Point estimates for disability progression were similar.

10.2.7 Summary of the Teva submission

Quality of the submitted systematic review and NMA were reasonable and appropriate, and findings matched in magnitude and direction, though not always in significance, with corresponding findings from the assessment group's NMAs. The assessment group did note challenges with the interpretation of the combined disability progression models, but found that inclusion of trials was reasonable and clear. However, there was a considerable lack of transparency about what inputs for each NMA model were, and no forest plots were presented. Additionally, it was not clear how dosages were used in the included models. NMAs were not presented for CIS.

10.3 *IFN β-1a 30 µg IM weekly (Avonex) and pegylated IFN β-1a 125 µg SC every two weeks (Plegridy) summary of Biogen submission*

10.3.1 Clinical effectiveness of Avonex in RRMS and CIS

The company submission stated that IFN β-1a 30 µg IM weekly is effective in reducing relapse rate and disability progression as compared to placebo, and cited MSCRG 1996[198] and its observational extension as evidence. The company submission further states that IFN β-1a 30 µg IM weekly is effective in delaying clinically definite MS in patients with CIS, and cites CHAMPS[170] and its open-label extensions in support of this.

10.3.2 RSS findings on clinical effectiveness of Avonex

Clinical effectiveness of Avonex in the RSS showed that in the year 10 analysis, [redacted]

10.3.3 Clinical effectiveness of Plegridy in RRMS

The company submission stated that pegylated IFN β-1a 125 µg SC every two weeks is effective in reducing relapse rate and disability progression as compared to placebo, and cited ADVANCE 2014,[211] as well as its extension, in support of this. Plegridy was not included in the RSS.

10.3.4 Our assessment of the Biogen submission

Our assessment of the systematic review contained in the Biogen submission can be found in Table 20.

Table 20: AMSTAR appraisal of the Biogen company submission

AMSTAR Checklist	**Manufacturer's submission**
1. Was an 'a priori' design provided?	Yes (Table 37 in the CS)
2. Was there duplicate study selection and data extraction?	Yes - the literature searches for this review were conducted as part of a wider program of research on treatments for MS. Search strategies included terms designed to identify studies of all EU approved treatments or treatments expected to be approved in the near future in either CIS, RRMS or SPMS patients. Identified studies were independently assessed by a reviewer in order to ascertain whether they met the pre-defined inclusion and exclusion criteria (based on population, interventions, comparators, and outcomes [PICOS]), and any uncertainties were resolved by discussion with a second reviewer. Data were extracted from eligible publications into a pre-defined table by a reviewer. All studies meeting the inclusion criteria described in Table 37 were initially included in the systematic review. These studies were then screened by two reviewers against the PICOS criteria of the NICE MTA of IFN-β and GA for treating multiple sclerosis to identify relevant studies for inclusion in meta-analyses and narrative syntheses.

3. Was a comprehensive literature search performed?	Yes - searches were conducted in October 2014 and updated on 9th November 2015 in MEDLINE (including MEDLINE In-process and MEDLINE Daily Update), Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Science Citation Index (SCI), with no restrictions on date. Using Boolean operators, the searches combined terms (including MeSH headings as appropriate) for the condition, the treatments and the outcomes of interest. A rapid appraisal was also conducted to identify relevant systematic reviews, technology appraisals, guidelines, and guidance in the following databases: Cochrane Database of Systematic Reviews (CDSR) Database of Abstracts of Reviews of Effects (DARE) Health Technology Assessment Database (HTA) National Institute for Health and Care Excellence (NICE) National Institute for Health Research (NIHR) Canadian Agency for Drugs and Technologies in Health (CADTH) International Prospective Register of Systematic Reviews (PROSPERO). In addition, searches were conducted in the clinical trial registers to identify data from ongoing or unpublished clinical trials: ClinicalTrials.gov, Current Controlled Trials, International Clinical Trials Registry Platform (ICTRP), PharmNetBund, and EU Clinical Trials Register (EUCTR). The full search strategies can be found in Appendix E. Hand searching of reference lists from included studies and relevant systematic reviews was also conducted.
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Unpublished trials were sought
5. Was a list of studies (included and excluded) provided?	Included: Yes - a summary of the 16 studies included in the MTC is provided in CS Appendix G (Table 55 in the CS). Details of studies included in the systematic review but excluded from the MTC are provided in CS Table 54 (CS Appendix F), along with rationale for their exclusion. Excluded: yes in CS Appendix
6. Were the characteristics of the included studies provided?	Yes – Appendix G in the CS
7. Was the scientific quality of the included studies assessed and documented?	Yes (Table 57 and Appendix G in the CS)
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Not stated

9. Were the methods used to combine the findings of studies appropriate?	Yes - sensitivity analyses took into account heterogeneity
10. Was the likelihood of publication bias assessed?	As stated in the report, 'Publication bias would have been assessed using funnel plots (e.g. SE (log [RR]) vs RR) where at least ten studies were included in an analysis; however, there were no head-to-head comparisons that included enough studies to produce a funnel plot.'
11. Was the conflict of interest included?	Manufacturer's submission

10.3.5 Review of network meta-analysis methods

Model type

Random effects and fixed effects models were both estimated and compared on the deviance information criterion, with random effects models preferred throughout. Further iterations were captured if convergence was in question.

Prior distributions and estimation

NMAs were estimated in the Bayesian framework using gemtc in the R environment. After 50,000 burn-in iterations, a further 50,000 iterations were captured. Convergence was assessed using the Brooks-Gelman-Rubin diagnostic. Prior distributions were non-informative.

Interventions

All studies testing comparisons between the drugs in the NICE scope and at the dosages contained in the marketing authorisation were included. Thus, dosages were clearly specified.

Outcomes and data preparation

Analyses included ARR for studies with follow-up of at least 12 months; HR for disability progression confirmed at 3 months and, separately, at 6 months, with follow-up data at 12 or 24 months; and for either any AE or serious AE. Data were analysed as log rate ratios, log hazard ratios or log odds ratios with corresponding standard errors. Authors do not provide a justification for models that were intended to be estimated at either 12 or 24 month follow-up, or why they chose to stratify estimates in this way. There is a lack of clarity regarding study inputs, and no forest plots for individual study estimates are presented.

Participants

Though the search included patients with RRMS, CIS and SPMS, it appears that only RRMS trials were meta-analysed.

Included trials

Studies excluded from the NMA and reasons for exclusion were clearly documented. However, the Biogen NMA excluded several studies on what would appear to be the basis of short-term follow-up. This is not made explicit.

10.3.6 Findings from the network meta-analysis presented in the company submission

The NMA found that IFN β-1a 30 µg IM weekly significantly reduced ARR relative to placebo, but not against other treatments. In fact, in the company submission NMA, GA 20 mg SC once daily was more effective in reducing ARR than IFN β-1a 30 µg IM weekly. Findings for disability progression confirmed at 3 or 6 months were not significant relative to other treatments or placebo.

The NMA found that for ARR, no significant treatment effects were observed between pegylated IFN β-1a 125 µg SC every two weeks and other treatments, or between pegylated IFN β-1a 125 µg SC every two weeks and placebo, though the last finding was marginally non-significant (RR=0.64, 95% CI [0.41, 1.04]). For sustained disability progression sustained for 3 or 6 months, no statistically significant differences were observed with pegylated IFN β-1a 125 µg SC every two weeks relative to other treatments or placebo.

Analyses for AEs were only conducted for IFN β-1a 30 µg IM weekly. No differences were found relative to placebo or other treatments.

Authors estimated a wide variety of sensitivity analyses summarised in CS Appendix H.

10.3.7 Results as compared to assessment group NMAs

Biogen's NMA on the whole did not identify statistically significant benefit from pegylated IFN β-1a 125 µg SC every two weeks or IFN β-1a 30 µg IM weekly on the key outcomes, which were ARR and disability progression confirmed at 3 months and at 6 months. However, both drugs demonstrated statistically significant effectiveness on each of these three outcomes in the assessment group's NMA. Point estimates were generally similar between the NMAs for ARR and time to disability progression confirmed at 3 months. This discrepancy may be due to the choice of prior distribution for between-trial variance in the base case of the company submission NMA, as well as the apparent exclusion of studies with short-term follow-up in the same. Notably, the assessment group considered several more drugs in the analysis of disability progression confirmed at 6 months than it would appear were included in the company submission's NMA for this outcome.

10.3.8 Summary of the Biogen submission

Quality of the submitted systematic review was both reasonable and appropriate. While a strength of the models was the explicit approach to dosages of comparators included, inputs in the NMA models were opaque and no study-level forest plots were presented with specific estimates. Moreover, the initial decision to stratify estimates by 12 or 24 months was not clearly explained, and apparent exclusions based on follow-up were not explicitly declared.

11 METHODS FOR ASSESSMENT OF COST EFFECTIVENESS STUDIES

11.1 *Identification of studies (clinically isolated syndrome)*

11.1.1 Introduction

The purpose of this systematic review was to identify existing cost-effectiveness model designs in CIS, and to identify parameter values (e.g. health state utilities and costs) suitable for use in a decision analytical model. We did not identify a suitable systematic review in CIS in the overview of systematic reviews (see Appendix 5) and scoping searches did not find many existing models. Therefore, our searches were broad and not limited by date.

11.1.2 Search strategy

The following electronic databases were searched: MEDLINE (Ovid); MEDLINE In-Process Citations and Daily Update (Ovid); Embase (Ovid); Cochrane Library (Wiley), including NHS EED, and HTA databases; Science Citation Index (Web of Knowledge), Research Papers in Economics (RePEC) and the Cost-effectiveness Analysis (CEA) Registry. The database searches were designed to be broad in nature, with search terms for CIS combined with terms for economic / HRQoL generic measures (based on recognised search filters[224-227]) where appropriate. A full record of searches is provided (see Appendix 6). The searches were not limited by publication date. All bibliographic records identified through the electronic searches and were collected in a managed reference database. The reference lists of included studies were also checked. Grey literature searches were undertaken using the online resources of various regulatory bodies, health service research agencies, professional societies and patient organisations and were undertaken concurrently for both clinical effectiveness and cost-effectiveness. For a record of these searches, see the clinical effectiveness record of searches in Appendix 1.

We undertook several additional searches. We checked the reference lists of primary studies identified through database searches for studies on the natural history of people with CIS, and CIS patient registries. We also undertook targeted database searches to identify any additional CIS patient registries including data from before 1995 (see Appendix 7). We searched studies citing included studies to identify more recent literature.

11.1.3 Inclusion and exclusion criteria

Studies meeting the following criteria were included in the review.

Population: Adults (≥18 years old) who have been diagnosed with CIS; defined as people who experienced a single demyelinating event in one or several areas of the central nervous system within the previous two months

Intervention: Disease modifying treatments (e.g. IFNβ-1a, IFNβ-1b) licensed for the treatment of CIS

Comparator: Best supportive care without DMTs or another DMT (e.g. IFNβ-1a, IFNβ-1b and glatiramer acetate) licensed for the treatment of CIS

Outcome: Cost per QALY, cost per life-year gained and cost per multiple sclerosis delayed

Study design: Economic analysis and included a decision analytical model

Language: English and Spanish

All publication types were included.

Other studies that contained information on parameter values (e.g. health state utilities, costs, natural history outcomes, etc.) suitable for use in a decision analytical model were identified at this stage and set aside for later review.

Studies in people diagnosed with relapsing remitting multiple sclerosis, secondary progressive multiple sclerosis, or primary progressive multiple sclerosis were excluded.

11.1.4 Study selection

Studies were first reviewed on title and abstract by two reviewers working independently (HM and PA). Subsequently, full-text studies were accessed and checked against the criteria for inclusion. As mentioned above, studies that presented information on costs and outcomes related to the natural history of or disease modifying treatment for people with CIS were also examined at this stage and set aside for later review.

11.1.5 Data extraction

Data extraction was conducted by two reviewers (HM and PA). Information extracted by one reviewer was cross-checked by the other. Any disagreements were resolved by discussion or by recourse to a third-party reviewer (JM). We extracted study details (title, author and year of study), background characteristics (population, intervention, comparator and outcomes), methods (study perspective, time horizon, discount rate, measure of effectiveness, assumptions and analytical methods), results (study parameters, base-case and sensitivity analyses), discussion (study findings, limitations of the models and generalisability) and other domains (source of funding and conflicts of interests). An example of the data extraction sheet is presented in Appendix 6.

11.1.6 Quality assessment

The studies were appraised using the Consolidated Health Economic Reporting Standards (CHEERS)[228] and Philips'[229] frameworks for best practice in economic evaluation and decision analytical modelling, respectively. The CHEERS assessment tool consists of six dimensions: title and abstract, introduction, methods, results, discussion and other. Under these dimensions/attributes, there are a series of questions to check whether these have been satisfactorily reported (see Appendix 6). The Philips reporting quality tool consists of two main dimensions: structure of the model and information used to parameterise the model. Under these dimensions/attributes there are a series of questions to check whether these have been satisfactorily conducted (see Appendix 6).

Reporting quality assessment was undertaken by two reviewers (HM and PA). Study quality assessed by HM was cross-checked by PA, and vice versa. Any disagreements were resolved by discussion or by recourse to a third-party reviewer (JM).

11.1.7 Data synthesis

Findings from included studies were synthesised narratively with the goal of summarising current modelling methods.

11.2 *Identification of studies (relapsing remitting multiple sclerosis)*

11.2.1 Introduction

The purpose of this systematic review was to identify existing cost-effectiveness model designs in RRMS, and to identify parameter values (e.g. health state utilities, costs etc.) suitable for use in a decision analytical model. We identified several related systematic reviews of cost-effectiveness evaluations in RRMS in the overview of systematic reviews.[230-238] Therefore, we performed searches for primary cost-effectiveness studies from the earliest search date found in these selected reviews (i.e. 2012) to April 2016. We performed separate searches for relevant HRQoL studies with no date limits applied. We used similar well-established methods which are used for undertaking systematic reviews of clinical studies,[162].

11.2.2 Search strategy

The following electronic databases were searched separately for cost-effectiveness studies and HRQoL studies: MEDLINE (Ovid); MEDLINE In-Process Citations and Daily Update (Ovid); Embase (Ovid); Cochrane Library (Wiley), including NHS EED, and HTA databases; Science Citation Index (Web of Knowledge), Research Papers in Economics (RePEC) and the Cost-effectiveness Analysis (CEA) Registry. The database searches were kept broad, with search terms for MS combined with terms for economics / HRQoL generic measures (based on recognised search filters[224-227]) where appropriate. A full record of searches is provided (see Appendix 7). The searches for primary cost-effectiveness studies were limited by publication date from January 2012 to April 2016. HRQoL searches were not limited by publication date. All bibliographic records identified through the electronic searches were collected in a managed reference database. The reference lists of included studies were also checked. Grey literature searches was undertaken using the online resources of various regulatory bodies, health service research agencies, professional societies and patient organisations.

The following additional searches were undertaken. We checked the reference lists of primary studies identified through the searches described in the paragraph above for studies on the natural history of people with RRMS, and RRMS patient registries. We also undertook targeted database searches to identify any additional RRMS patient registries that include data from before 1995 (see Appendix 7). Citation searches on any included studies was undertaken to identify more recent literature.

11.2.3 Inclusion and exclusion criteria

Studies meeting the following criteria were included in the review:
Population: Adults (≥18 years old) who have been diagnosed with relapsing remitting multiple sclerosis
Intervention: IFNβ-1a, pegylated IFNβ-1a, IFNβ-1b or GA

Comparator: Best supportive care without DMTs or another DMT (e.g. IFNβ-1a, IFNβ-1b and glatiramer acetate) licensed for the treatment of RRMS
Outcome: Cost per QALY, cost per life-year gained and cost per multiple sclerosis delayed
Study design: Economic analysis comprising of a decision analytical model

Other studies that contained information on parameter values (e.g. health state utilities, costs, natural history outcomes, etc.) suitable for use in a decision analytical model were identified at this stage and set aside for later review.

Studies were excluded if they included people diagnosed with clinically isolated syndrome. Additionally studies were excluded if they were reported in a form of an abstract or conference proceeding, or not published in the English language.

11.2.4 Study selection

Studies were first reviewed on title and abstract by two reviewers working independently (HM and PA). Subsequently, full-text studies were accessed and checked against the criteria for inclusion. As mentioned above, studies that presented information on costs and outcomes related to the natural history of or disease modifying treatment for people with RRMS were also examined at this stage and set aside for later review.

11.2.5 Data extraction

Data extraction was conducted by two reviewers (HM and PA). Information extracted by one reviewer was cross-checked by the other. Any disagreements were resolved by discussion or by recourse to a third-party reviewer (JM). We extracted study details (title, author and year of study), background characteristics (population, intervention, comparator and outcomes), methods (study perspective, time horizon, discount rate, measure of effectiveness, assumptions and analytical methods), results (study parameters, base-case and sensitivity analyses), discussion (study findings, limitations of the models and generalisability) and 'other' (source of funding and conflicts of interests). An example of the data extraction sheet is presented in Appendix 7.

11.2.6 Quality assessment

The studies were appraised against the Consolidated Health Economic Reporting Standards (CHEERS)[228] and Philips'[229] frameworks for best practice in economic evaluation and decision analytical modelling, respectively. The CHEERS assessment tool consists of six dimensions: title and abstract, introduction, methods, results, discussion and other. Under these dimensions/attributes, there are a series of questions to check whether these have been satisfactorily reported (see Appendix 7). The Philips' reporting quality tool consists of two main dimensions: structure of the model and information used to parameterise the model. Under these dimensions/attributes there are a series of questions to check whether these have been satisfactorily reported (see Appendix 7).

Reporting quality assessment was undertaken by two reviewers (HM and PA). Studies quality assessed by one reviewer was cross-checked by the other. Any disagreements were resolved by discussion or by recourse to a third-party reviewer (JM).

11.2.7 Data synthesis

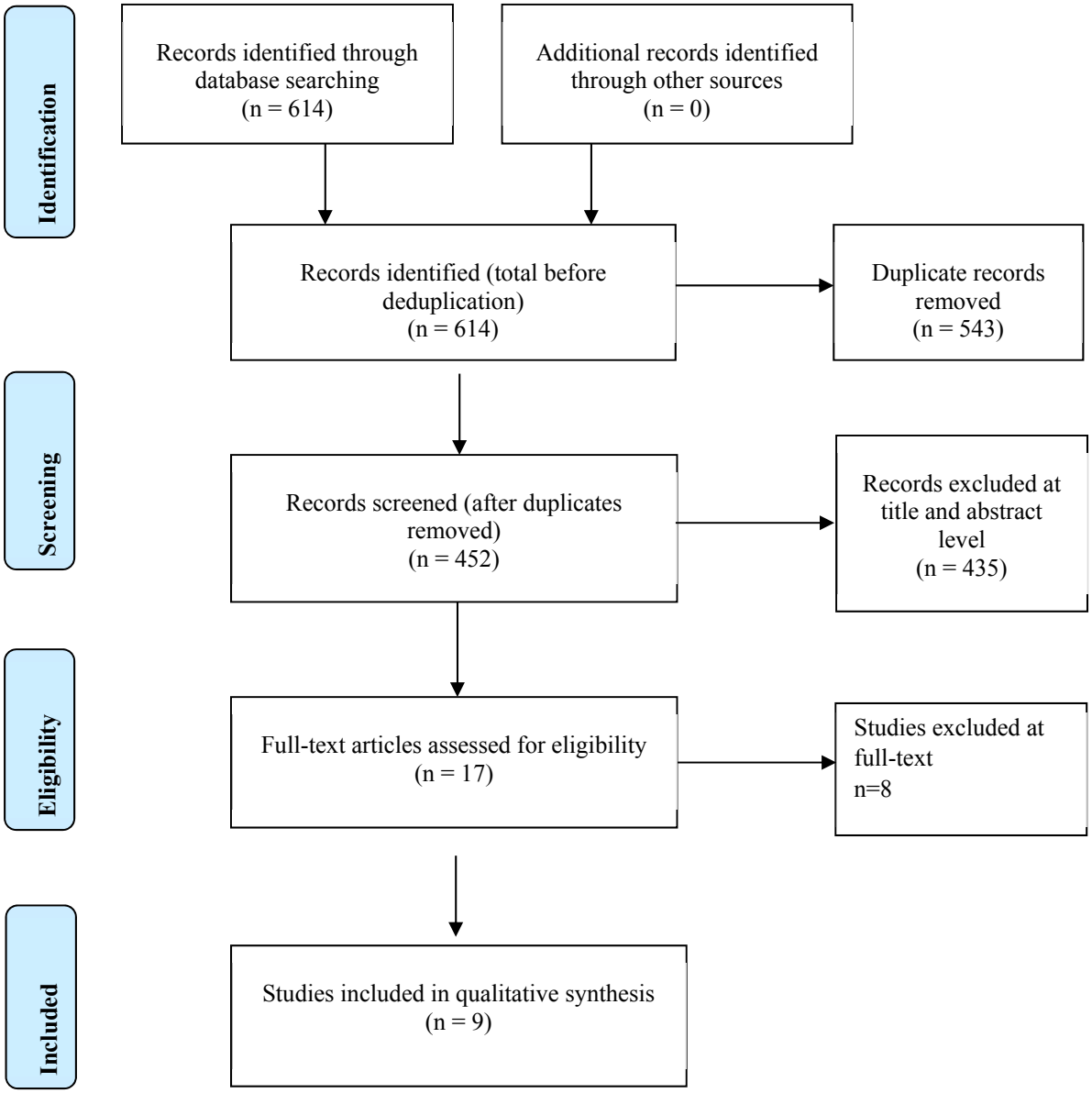
Information extracted from the included studies was summarised in a table. The findings from these studies have been compared narratively to show the current modelling methods used, and our recommendations for future modelling of RRMS are discussed.

12 RESULTS OF THE SYSTEMATIC REVIEW OF THE COST EFFECTIVENESS LITERATURE

12.1 *Results of search for clinically isolated syndrome studies*

The electronic database searches identified 614 records (Figure 24). After removing duplicates, 452 records were screened for inclusion. On the basis of title and abstract, 435 records were excluded and the remaining 17 records were included for full-text screening. A further 8 articles were excluded at the full-text stage, with the reasons for exclusion in Appendix 6, leaving nine studies[239-247]that included a decision-analytical model, which was used to estimate the cost-effectiveness of DMTs for treating people with CIS.

Figure 24: PRISMA flowchart for economic studies relating to CIS



12.2 *Description of included studies*

12.2.1 Summary of economic studies comparing DMTs for people with CIS

Fredrikson[239]

Fredrikson et al.[239] used a Markov model structure to assess the cost-effectiveness of subcutaneous IFNβ-1a three times weekly compared to no treatment for people who had experienced a single demyelinating event in one or several areas of the central nervous system within the previous two months. The model simulated the pathway for people with CIS who received disease modifying treatment versus no treatment, and the cost-effectiveness was estimated over the model's time horizon. The model started with a hypothetical cohort with a mean age of 31 years, which reflected the participants in the REFLEX trial and continued with those occupying/progressing to one of the following health states (CIS and on treatment, CIS no treatment or RRMS defined by the McDonalds 2005 criteria). Fredikson and colleagues made a number of simplifying assumptions (once people converted to RRMS, they could progress in single step increments, treatment effect was assumed to continue over the model time horizon, based on clinical judgment, a maximum duration of 25 years for treatment was applied, the probability of discontinuation of disease modifying treatment (DMT) was derived based on the three-year rate from the REFLEXION trial. This probability was applied from year 3 to the remainder of the model duration, authors assumed that 95% of people with CIS would convert to MS using the McDonald's criteria and people with MS who progressed to EDSS 7 or converted to SPMS were assumed to discontinue treatment).

Information required to populate the model was obtained from REFLEX and REFLEXION trials, and resource use and costs from published sources. Information was required on utility values associated with CIS and MS (by EDSS state), conversion rate from CIS to CDMS according to McDonald MRI criteria, annual average drop-out rate during 25 years, market share of disease modifying treatment for MS. Resource use and costs included: informal care, services, investments (house and car modifications, walking aides, wheelchairs), symptom management medication, tests (MRI scans of the brain and spinal cord in the first year of diagnosis and a brain MRI scan every year), ambulatory care, inpatient care, loss of productivity due to early retirement and short-term absence. The analysis was conducted from the societal perspective, and the results presented in terms of costs per progression-free life-years and costs per QALY gained over a 40-year time horizon. All costs were reported in Swedish Kronor, 2012 prices and converted to Euros using a historical average exchange rate from 2005. All costs and outcomes were discounted 3% per annum. Along with the cost-effectiveness analysis, Fredrikson and colleagues conducted univariate and probabilistic sensitivity analyses.

Results in terms of progression-free life-years gained, showed that there was an incremental gain of 1.63 progression-free life-years for people who received DMT compared with no treatment. Additional, the results showed that there was a 0.53 incremental QALY gain for people who received treatment. From the societal perspective, the base-case results showed cost-savings of approximately SEK 270,260.

Kobelt[240]

Kobelt and colleagues[240] used a Markov structure to assess the cost-effectiveness of using interferon beta-1b SC 250 µg every other day (betaferon) compared with no treatment for people with CIS. The model simulated the disease progression for a hypothetical cohort of people being treated for CIS and the cost-effectiveness was estimated over a 20-year time horizon. The model started with a cohort of people who received either interferon beta-1b SC 250 µg every other day (betaferon) or no treatment and continued with them remaining in the CIS health state or progressing to mild, moderate or severe multiple sclerosis disability. An illustrative Markov structure was not presented as this was an abstract.

Authors did not elaborate on the sources of information used to populate the model. All costs were reported in 2006 Euros. The primary outcome measure of effectiveness was QALYs gained over the 20-year time horizon; however, the author did not elaborate on the descriptive tools used to value these health states. All costs and benefits were discounted at 3% per annum. The analysis was conducted from the societal perspective and results were presented in terms of an incremental cost-effectiveness ratio (ICER) expressed as cost per QALYs gained. Kobelt[240] conducted sensitivity analyses by changing key model input parameters to determine the impact on the deterministic results. Additionally, a probabilistic sensitivity analysis (PSA) was undertaken.

Base-case results showed that interferon beta-1b dominated the no treatment arm. The results from the sensitivity analyses showed that the base-case results were robust to changes in model input parameters. Results from the probabilistic analysis showed that interferon beta-1b was the preferred option, with >0.5 probability of being cost-effective compared with no treatment at a willingness-to-pay threshold of 50,000€ per QALY.

Lazzaro[241]

Lazzaro and colleagues[241] developed an epidemiological/survival model to estimate the cost-effectiveness of interferon beta-1b SC 250µg every other day (Betaferon) for people with mono and multifocal CIS diagnosis compared with postponing disease modifying disease treatment until subsequent conversion to clinically definite multiple sclerosis.

Information required to populate the model was obtained from published sources. Information on incidence of CIS, utility value of CIS, conversion rate from CIS to CDMS according to McDonald magnetic resonance imaging (MRI) criteria, annual average drop-out rate during 25 years was obtained. All resource use and costs (disease modifying drugs and other drugs, outpatient diagnostic procedures, consultations and laboratory tests, hospitalization, physical therapy, walking aids, transport, working days lost by patients and their caregivers and informal care) were obtained from published sources and presented in Euros, 2006 prices. Results were presented in terms of an ICER and expressed as cost per QALYs gained over the 25-year time horizon. Measurement and valuation of preference-based outcomes have not been reported. The base-case analysis was undertaken from the Italian National Health Service (INHS) perspective and all costs and benefits were discounted at 3% per annum. To have a workable model, a number of simplifying assumptions were made. Authors undertook a number of one-way (annual consumption of and average annual compliance rate to IFN β-1b SC 250µg every other day (Betaferon); replacement of IFN β-1b with IFN β-1a SC 44 µg three days a week;

CDMS-related patient utility values) and multi-way (annual conversion rates to CDMS during year 1 and 2) sensitivity analyses, and also conducted probabilistic sensitivity analysis.

From the INHS perspective, the base-case results showed that the mean incremental costs per for people who received early treatment compared to delayed treatment was approximately 894€. Mean incremental gain for people who received early treatment compared to delayed treatment was 0.35, which equated to an ICER of approximately €2575 per QALY. From the societal viewpoint, early treatment dominated delayed treatment, meaning that early treatment was cheaper than delayed treatment and more effective. Results from the one-way and multi-way sensitivity analyses showed that the base-case results were sensitive to the change in the DMTs, and the lower limit 95% confidence intervals CDMS conversion rates during years 1 and 2 of the epidemiological model. Results from the probabilistic sensitivity analysis showed that at a €5500 willingness-to-pay for an incremental QALY, early treatment is likely to be cost-effective with a probability of 1.

Iskedjian[242]

Iskedjian 2005[242] used two Markov model structures to assess the cost-effectiveness of intramuscular IFN β-1a 30 µg once weekly (Avonex) compared to current treatment (methylprednisolone four intravenous injections of 1g for three days followed by 14 days of oral steroids 1mg twice daily) for people who had experienced a single, clinically diagnosed, demyelinating event. The model simulated the pathway for people with CIS who received DMTs versus symptom management, and the cost-effectiveness was estimated over a 12-year time horizon. The first model started with a hypothetical cohort of people receiving one of the two treatments and captured the costs and outcomes associated with the progression to clinically definite multiple sclerosis, and the second model estimated the long-term costs and outcomes of progression through various EDSS states [mild (EDSS ≤ 3.5), moderate (EDSS 4-5.5) and severe (EDSS ≥ 6)]. Iskedjian and colleagues made a number of simplifying assumptions; for example, people who progressed to clinically definite multiple sclerosis received no treatment benefit but accrued costs associated with their EDSS health states, people in both arms of the model received Avonex (IFN β-1a 30µg once weekly intramuscularly) once diagnosed with CDMS. Relapse rates were fixed to one every two years, relapses were assumed to last for two months and people did not discontinue from treatment (i.e. 100% compliance was assumed).

Information on transition probabilities resource use and costs were obtained from the literature. The analysis was conducted from the Canadian Ministry of Health and societal perspectives, and the results presented in terms of costs per Mono-symptomatic life years (MLY) gained, and QALYs gained over a 12-year time horizon. Utility values were derived based on the Health Utility Index (HUI) questionnaire, which was administered to Canadian MS patients. A separate analysis was undertaken, which used utility values derived from the EQ-5D questionnaire. All costs were reported in Canadian dollars, 2001 prices. All costs and outcomes were discounted by 5% per annum. Along with the cost-effectiveness analysis, Iskedjian and colleagues conducted univariate (20 and 30 year time horizons, using utility values based on EQ-5D questionnaire and varying the discount rate) and probabilistic sensitivity analyses.

Results from the Canadian Ministry of Health perspective showed that over the 12-year time horizon mean costs were CAN$173,000 and $108,000 for the Avonex (IFN β-1a 30µg once weekly intramuscularly) and the current

treatment arm, respectively. Expected mean mono-symptomatic life years gained were 4.69 and 3.48 for the IFN β-1a (Avonex) and the comparator arm, respectively, which equated to an ICER of CAN$53,110 per MLY gained. Results from the societal perspective showed that over the 12-year time horizon mean costs were CAN$317,000 and $262,000 for the Avonex and current treatment arms. Expected mean mono-symptomatic life years gained was 4.69 and 3.48 for the IFN β-1a (Avonex) and current treament arms. which equated to an ICER of approximately CAN$44,800 per MLY gained. The ICERs per QAMLY gained were approximately CAN$227,600 and CAN$189,300 from the Ministry of Health and societal perspective, respectively. Using utilities derived from the EQ-5D, the ICERs per QAMLY gained were approximately CAN$116,100 and CAN$91,200 from the Ministry of Health and societal perspective. Sensitivity analysis results demonstrated that in the progression to clinically definite multiple sclerosis model, the results were sensitive to the time horizon and the rate of progression the clinically definite multiple sclerosis. Using a six-year time horizon resulted in an incremental cost per MLY gained of CAN$85,100 and CAN$79,300 for the Ministry and societal perspective. Increasing the probability of progressing to clinically definite multiple sclerosis reduced the incremental cost per MLY gained to CAN$44,700 and CAN$35,600 for the Ministry of Health and societal perspective, respectively. Decreasing the probability to progression to clinically definite multiple sclerosis resulted in an increase in the incremental cost per MLY gained to CAN$67,800 and CAN$60,200 for the Ministry of Health and societal perspectives.

Arbizu[243]

The study by Arbizu et al.[243] was presented as an abstract from conference proceedings. Arbizu et al undertook a cost-utility analysis comparing the costs and consequences of providing supportive care to treatment with IFN β-1b in Spanish patients who have incident CIS. They estimated the costs from the societal perspective and adjusted to 2008 Euros. A 3% discount rate was applied to future costs and health benefits. They used a Markov model and EDSS scores defined initial health states. In their analyses they assumed that those who progressed to RRMS would start IFN β-1b and would remain on treatment until EDSS worsened to 6.5. The BENEFIT trial findings were used to model EDSS progression over time and transitions from CIS to MS. Cost and utility scores were predominantly obtained from published sources.

Their main findings suggest that when the model was run over a 50-year time horizon the ICER of IFN β-1b versus no treatment was €20,500/QALY gained. Their findings were sensitive to time horizon, IFN β-1b cost and risk of disease progression on treatment.

Caloyeras[245]

The study by Caloyeras et al.[245] is presented as an abstract of conference proceedings. Caloyeras et al[245] undertook a cost-utility analysis comparing the costs and consequences of providing supportive care to treatment with IFN β-1b in Australian patients who have incident CIS. They used findings from the BENEFIT study to determine initial EDSS scores for those with CIS, subsequent risk of progression in EDSS scores and risk of progressing to RRMS. They estimated the costs from the societal perspective and adjusted to 2007 Austrailian dollars (AUD). A discount rate of 5% was applied to discount future costs and health benefits, in accordance with Australian policy guidelines. They used a Markov model and EDSS scores defined initial

health states for CIS and RRMS. The costs and utilities attached to treatment health states for CIS and RRMS were identical, and dependent on the EDSS score. DMTs were assumed to discontinued, when disability worsened to EDSS score 6.5. Published sources were used to estimate costs and utility weights for health states.

When the model was run over a 25-year time horizon the ICER of IFNB-1b versus supportive care was AUD 20,000 (USD 14,000) per quality-adjusted life year (QALY) gained.

Caloyeras[244]

The study by Caloyeras et al[244] is presented as an abstract of conference proceedings, with poster presentation retrieved for appraisal. Caloyeras et al undertook a cost-utility analysis comparing the costs and consequences of providing supportive care to treatment with IFN β-1b in Australian patients with incident CIS. They used findings from the BENEFIT trial to determine initial EDSS scores for those with CIS, subsequent risk of progression in EDSS scores and risk of progressing to RRMS. They estimated the costs from the societal perspective and adjusted to 2007 AUD. A national guideline of 5% was applied to discount future costs and health benefits. They used a Markov model and EDSS scores defined initial health states for CIS and RRMS. The costs and utilities attached to treatment health states for CIS and MS were same, and dependent on EDSS score. DMTs were assumed not to discontinue, unless disability worsened to EDSS score 6.5. Patients were limited to one adverse event per annum.

Their main findings suggest that when the model was run over a 25-year time horizon the ICER of IFN β-1b versus no treatment was AUD 68,000 per QALY gained.

It is of note that these findings are presented by the same group as Caloyeras et al[245]. A different of cost per QALY was derived given even though it appears as though the same setting/perspective, time horizon, model structure and underlying trial data from the BENEFIT trial were used.

Caloyeras[246]

Caloyeras et al.[246] used a Markov model structure to assess the cost-effectiveness of IFN β-1b (250 µg once daily) compared to best supportive care for people with their first clinical event suggestive of MS. The model simulated the pathway for people with CIS who received DMTs versus best supportive care, and the cost-effectiveness was estimated over the model's time horizon. The model started with a hypothetical cohort of people 30 years old who were diagnosed with CIS and had an EDSS level of 0-5.5, and continued with people occupying/progressing to one of the following seven health states (Markov model with seven health states (EDSS 0.0, EDSS 1.0-1.5, EDSS 2.0-2.5, EDSS 3.0-3.5, EDSS 6.0-7.5 non-relapse, EDSS 8.0-9.5 non-relapse and EDSS 10 (MS-related death)). Caloyeras and colleagues made a number of assumptions (progression in EDSS levels modelled independently of progression to MS; two types of relapses modelled: relapse resulting in progression from CIS to MS and relapse after progression to MS; all–cause mortality estimated using life tables; MS specific mortality only when EDSS score 10 and people who discontinued treatment did not restart DMTs).

Clinical information (e.g. hazard ratios for DMTs compared with placebo) required to populate the model was obtained from the BENEFIT trial. Information on utility associated with EDSS levels was obtained from published sources. Resource use and costs included hospital inpatient care, ambulatory care, tests, drugs (DMTs

and other drugs), services, adaptations/investments and costs of informal care. Costs associated with relapses were estimated from a cross-sectional web-based survey. The analysis was conducted from the Swedish societal perspective, and the results presented in terms of costs per QALY gained over a 50-year time horizon. All costs were reported in Swedish kronor, 2009 prices. All costs and outcomes were discounted 3% per annum. Along with the cost-effectiveness analysis, Caloyeras and colleagues have undertaken one-way sensitivity analysis (acquisition costs, EDSS threshold for discontinuation, time horizon of the model, EDSS progression probability and discount rates) and probabilistic sensitivity analysis (drug acquisition costs, direct and indirect costs, utilities, EDSS progression probabilitieis, treatment discontinuation rate, relaspse rate) using uniform distribution and varying model parameters by ±2.5%.

Base case results showed that treatment with IFN β-1b dominated the best supportive care arm (commencing treatment when people progressed to RRMS). People who started on early treatment accumulated slightly higher direct medical costs per patient, but lower direct non-medical costs. Results from the sensitivity analyses demonstrated that the base case results were robust to changes made to model parameters. However, the model findings were sensitive to changes made to the time horizon of the analysis. Undertaking the analysis over a shorter 5-year time horizon found, early treatment was not cost-effective (1.32 million SEK).

Zarco[247]

Zarco and colleagues[247] used a decision tree structure to assess the cost-effectiveness of IFN β-1a or IFN β-1b compared to best supportive care for people who are diagnosed with clinically isolated syndrome. The model started with a hypothetical cohort of people with CIS and continued with a proportion of people having a relapse or not having a relapse at a one-year time horizon. At the two-year time horizon, the model considers the proportion of people who progressed to CDMS and those remaining in a CIS health state. The report was unclear on the assumptions made in the model.

Infromation on the progression from CIS to CDMS in an untreated population was obtained from the BENEFIT trial. Information on treatment efficacy of disease modifying treatments was obtained from clinical trials. Resource use and costs were estimated from a hospital-level micro-costing study and treatment costs were estimated from national health incurance. The analysis was conducted from the Columbian societal perspective, and the results presented in terms of costs per QALY and cost per diability adjusted life years over a 2-year time horizon. All costs were reported in USA dollars, 2011 prices. All costs and outcomes were discounted in the second year by 3%. Authors have undertaken univariate and probabilistic sensitivity analyses.

Base-case results in terms of cost per QALY showed that interferons were not cost-effective when compared to best supportive care for treating people with clinically isolated syndrome.

Table 21: Characteristics of included economic evaluations in CIS

Author, year and country	Attributes										
	Population	**Intervention and comparator**	**Perspective**	**Model type and cycle length**	**Health states**	**Time horizon**	**Evidence synthesis**	**Outcomes**	**Source of preference data**	**Discount rate**	**Sensitivity analysis**
Fredrikson et al.[239] Sweden	People who experienced a single demyelinating event in one or several areas of the central nervous system within the previous two months	SC IFN β-1a three-times weekly compared to no treatment	Societal perspective	Cohort Markov model with one-year cycle length	CIS and on treatment, CIS no treatment or relapsing-remitting multiple (RRMS) defined by the McDonalds 2005 criteria	40-year time horizon	Not based on a systematic review	Progression free life years, quality-adjusted life years	Not reported (authors suggested that utility values associated with each EDSS level were obtained from a study in MS patients	3% per annum for costs and outcomes	RRMS defined by the Poser criteria
Kobelt et al.[240] Sweden	People with a clinically isolated event	IFN β-1b compared to no treatment	Societal perspective	Cohort Markov model with one-year cycle length	Progression from CIS to mild, moderate and severe MS	20-year time horizon	Not reported	Quality-adjusted life-years gained	Not reported	3% per annum for costs and outcomes	Changes to time horizon, treatment duration and the proportion of people treated at conversion
Lazzaro et al.[241] Italy	People with mono and multifocal CIS diagnosis (McDonald criteria)	IFN β-1b SC 250µg every other day compared to no treatment	Italian National Health Service and Societal perspectives	Epidemiological/survival model	Not reported	25-year time horizon	Not reported	Quality-adjusted life-years gained	Not reported	3% per annum for costs and outcomes	Annual consumption of and average annual compliance rate to IFNβ-1b;

Author, year and country	Attributes										
	Population	**Intervention and comparator**	**Perspective**	**Model type and cycle length**	**Health states**	**Time horizon**	**Evidence synthesis**	**Outcomes**	**Source of preference data**	**Discount rate**	**Sensitivity analysis**
											replacement of IFN β-1b with 44 µg IFN β-1a SC three days a week; CDMS-related patient utility values), and PSA
Iskedjian et al.[242] Canada	People who experienced a single, clinically diagnosed, demyelinating event	IFN β-1a (Avonex) 30µg intramuscular injections once weekly compared to Methylprednisolone four intravenous injections of 1g for three days followed by 14 days of oral steroids 1mg twice daily	Ministry of Health and societal perspectives	Two cohort Markov models each with one-year cycle lengths	The first model captured costs and outcomes associated with progression to CDMS and the second model estimated the long-term costs and outcomes of progression through various EDSS states [mild (EDSS ≤ 3.5), moderate (EDSS 4-5.5)	12-year time horizon	Not reported	Mono-symptomatic life-years gained, quality-adjusted life- years gained	Utility values were derived based Health Utility Index (HUI) questionnaire and utility values derived based on EQ-5D questionnaire	5% per annum on costs and outcomes	20 and 30 year time horizons, using utility values based on the EQ-5D questionnaire, varying discount rates

Author, year and country	Attributes										
	Population	**Intervention and comparator**	**Perspective**	**Model type and cycle length**	**Health states**	**Time horizon**	**Evidence synthesis**	**Outcomes**	**Source of preference data**	**Discount rate**	**Sensitivity analysis**
					and severe (EDSS ≥ 6)]						
Arbizu et al[243] Spain	People with clinically isolated syndrome	IFN β-1b (250µg every other day) versus no treatment	Not reported	Not reported	Not reported	50 years	Not reported	QALYs	Not reported	3% per annum on costs and benefits	SA has been undertaken but it was unclear on the extent
Caloyeras et al[244] Australia	Adults with clinically isolated syndrome	IFN β-1b (250µg every other day) versus best supportive care	Societal	Markov model	CIS health states and RRMS health states defined by same EDSS strata (0; 1-1.5; 2-2.5; 3-5.5; 6).	25 years	Based on results from a randomised controlled trial	QALYs	EQ-5D data from BENEFIT RCT and published literature	5% per annum on costs and benefits	Unclear but looks like one-way sensitivity analysis only
Caloyeras et al.[245] Australia	Adults with clinically isolated syndrome	IFN β-1b (250µg every other day) versus best supportive care	Australian perspective but unclear if health provider or societal	Markov model	Health states defined by EDSS levels	25 years	Based on results from a randomised controlled trial	QALYs	Obtained from published studies	5% per annum on costs and benefits	Unclear but looks like one-way sensitivity analysis only
Caloyeras et al.[246] Sweden	Patients with first clinical event suggestive of MS (CIS)	IFN β-1b (250mcg every other day) versus best supportive care	Societal	Markov model	First clinical event suggestive of MS (EDSS 0 to 5.5), RRMS (EDSS 0 to 5.5), Non-relapsing	50 years	Based on results from a randomised controlled trial	QALYs	EQ-5D data from BENEFIT RCT and published literature	3% per annum on costs and benefits	Univariate and probabilistic sensitivity analyses

Author, year and country	Attributes										
	Population	**Intervention and comparator**	**Perspective**	**Model type and cycle length**	**Health states**	**Time horizon**	**Evidence synthesis**	**Outcomes**	**Source of preference data**	**Discount rate**	**Sensitivity analysis**
					forms of MS (EDSS 6 to 9.5) and EDSS 10 (Dead) and Dead from all-causes						
Zarco et al.[247] Columbia	People meeting standard indication for initiation of treatment with IFN β-1a, and have a diagnosis of CIS/MS	IFN β-1a and IFN β-1b	Societal	Decision tree	Conversion to MS	Two years	Unclear	DALYs and QALYs	Obtained from published tables	3% on costs and outcomes in the second year	Relapse management, conversion probabilities, and indirect costs; probabilistic sensitivity analysis

CDMS, clinically definite multiple sclerosis; CIS, clinically isolated syndrome; EDSS, expanded disability status scale; EQ-5D, euroQol five dimensions; HUI, health utility index; RRMS, relapsing-remitting multiple sclerosis; SC, subcutaneous; RRMS,

12.2.2 Characteristics of the included studies

The characteristics of the studies included in this review are presented in Table 21. All of the studies included an economic model to estimate the cost-effectiveness of using DMTs for treating people with CIS. The economic evaluations were conducted in Sweden[239, 240, 246], Australia[244, 245],Italy[241], Colombia[247], Spain[243] and Canada[242].

Studies[239-241, 244-246] mainly compared disease modifying treatments compared with no treatment. One study[247] compared IFNβ-1a with IFNβ-1b. Treatment included IFNβ-1a subcutaneous three-times weekly[239], subcutaneous IFNβ-1b[240, 241, 243-245]. However, one study[242] compared DMTs (INFβ-1a 30µg intramuscular injections once weekly) versus current treatment (methylprednisolone four intravenous injections of 1g for three days followed by 14 days of oral steroids 1mg twice daily).

Six studies[239, 240, 242, 244-246] used a cohort Markov model structure and one study[241] used an epidemiological/survival model and affixed costs and benefits accrued over time for occupying health states. One study[243] used a decision tree structure, and in the remaining study, it was unclear on the model structure used. Model cycle lengths ranged from six months[246] to one year, and time horizons ranged from 12 years[242] up to 50 years[246]. Most studies[239, 240, 242, 244-246] included longer term progression through to relapsing-remitting multiple sclerosis and estimated the cost-effectiveness.

Four studies[239, 240, 244, 246] analysed cost-effectiveness from the societal perspective, whereas two studies[241, 242] analysed from both the health service and the societal perspectives. Two studies[243, 245] were unclear on the perspective of the analysis. Five studies[239-241, 243, 246] used a discount rate of 3% per annum for costs and outcomes, while three studies[242, 244, 245] applied an annual 5% discount rate for costs and outcomes. Six studies[240, 241, 243-246] presented their results in terms of cost per QALY alone and the remaining two studies used progression-free survival[239] and mono-symptomatic life-years gained[242] in addition to cost per QALY.

12.2.3 Definition of clinically isolated syndrome

The definitions used to characterise people with CIS were consistent. The majority of the studies defined their hypothetical cohort as adults who had experienced a single demyelinating event suggestive of multiple sclerosis. Two studies[239, 241] elaborated on this definition and suggested their cohorts referred to adults who experienced a single demyelinating event in one or several areas of the central nervous system. To our knowledge, no studies included in this systematic review defined their population based on the McDonald 2010 criteria.

12.2.4 Characteristics of clinically isolated syndrome models

Four studies[239, 240, 242, 246] modelled the longer-term impact of treating CIS with DMTs incorporating progression to RRMS. No studies modelled conversion from RRMS to SPMS. All studies except the one conducted by Iskedjian and colleagues[242] considered progression until death in the analysis, but there was no justification for omitting this health state in the analysis. Disease progression in the RRMS health states was stratified by severity (mild, moderate and severe)[240, 242] or by predicting changes in EDSS levels[239, 241, 243-246]. In the majority of the studies the risk of death was obtained from country-specific lifetime tables for the general population. In one study[239], mortality rates were adjusted to reflect the increase risk of mortality associated with multiple

sclerosis. Here, background mortality was multiplied by EDSS-specific adjustment factors to reflect MS-specific mortality. All other studies accounted for death by assuming people died on progression to EDSS 10. Adjusting the background mortality and including progression to EDSS 10 leads to double counting of people who may die from MS-related causes.

12.2.5 Treatment effect of disease modifying treatments in the CIS health state

Three studies[239, 241, 246] clearly stated that treatment discontinuation was considered in analysis. One study[242] assumed that people did not discontinue treatment. The remaining studies[240, 243-245] were unclear on whether treatment discontinuation was included in the analysis. Treatment discontinuation was assumed to be a result of adverse events from drug utilisation, and/or progressing to EDSS ≥6. Discontinuation rates ranged from 6% every two years[239] to 17.7% annually[241]. It appeared that Fredrikson and colleagues[239] assumed a constant hazard over time for discontinuation of treatment in the first two years, and in subsequent years used information from a follow-on trial. In the analysis undertaken by Caloyeras and colleagues[246], these authors fitted a Weibull parametric model to Swedish registry data to derive time dependent transition probabilities for people discontinuing treatment. Here, discontinuation of treatment was assumed to be the same for both early and delayed treatment (waiting until people developed MS).

12.2.6 Quality assessment of the modelling methods in CIS studies

In this section we present a summary of the reporting quality of the studies included in the current review against the Philips' checklist presented in Appendix 6.

Structure

Models presented in full publications were generally of good quality. The studies clearly stated their decision problem, the perspective of the analysis, and the objectives of the model analysis, all of which were consistent with the decision problem and disease progression. However, analyses were often limited in scope. Most studies compared one DMT with best supportive care, thus not including and analysing all treatment options available for people with CIS. All studies clearly stated the time horizon of their analysis, but studies with shorter time horizons may not have been able to capture all the costs and conseqeunces of treating or not treating CIS with DMTs.

Information required for models

In general, methods used in the published studies to identify relevant information to populate the models were satisfactory[239, 241, 242, 246, 247]. As expected, less information was available from published abstracts[240, 243-245]. All studies provided references for their model inputs, but authors were not clear on how the evidence was synthesised (e.g. search strategy, quality assessment). In all studies, information was required on the effect of DMTs on disease progression, resource use and costs, outcomes and mortality. The effect of DMTs on delaying progression from CIS to RRMS was modelled using hazard ratios. The relative reduction in progression which was associated with DMTs was then applied to the predicted baseline cohort of people with CIS. All studies[239-246] except Zarco et al.[247] derived a hazard ratio directly from a trial. In contrast, Zarco and collegaues obtained

this hazard ratio by combining the treatment effects from a number of studies. However, these authors did not elaborate on the quality assessment of these RCTs or on how information on treatment effects was meta-analysed. The effect of DMTs can be applied to a baseline cohort of people to show the treatment effect on conversion to RRMS. Baseline information can be obtained from CIS registries, natural history cohort or from a placebo arm of a clinical trial. In all studies, information on disease progression in a baseline cohort was obtained from RCTs. Most studies have undertaken analyses based on a long time horizon, which is in line with the NICE reference case. However, only two studies[239, 246] elaborated on the techniques used to extrapolate treatment effects beyond the time horizon of the RCTs. These studies provided information on the parametric models chosen, and justified their choice of survival model.

Most studies[239, 241, 242, 246, 247] justified and referenced costs used in their analyses. Costs required for the models were mainly obtained from published sources, and these were inflated to current prices using the appropriate indices. In some studies[241, 246], authors provided detailed information on resource use. All authors stated the perspective of the analyses, and the resource use and costs reflected the viewpoint/perspective of the analyses. All authors discounted costs and benefits using the appropriate rates.

In the models that reported their results in terms of QALYs, authors provided the references used to obtain the utility weights. However, the majority of the authors did not elaborate on the descriptive tools/measures used to value these health states in these populations, or have not elaborated on the quality assessment or choices made between sources. Additionally, authors did not elaborate whether or not sources of utility information used were relevant to their population of interest. To our knowledge, utility weights were obtained primarily from studies undertaken in an RRMS population.

Uncertainty

All studies addressed parameter uncertainty in their analyses, but none attempted to address all types (methodological, structural, parameter and generalisability) of uncertainty. All studies made changes to key model input parameters to explore the impact on the results. Two studies[240, 242] ran their analysis over shorter time horizons to explore impact on ICER estimates. However, it was unclear if these studies also assumed that the duration of the treatment effect had been reduced.

12.3 *Summary of CIS cost-effectiveness evidence*

The evidence base offers insight into the decision analytical models used to estimate the cost-effectiveness of DMTs for reducing the conversion to multiple sclerosis. We identified nine studies, which included six full text articles and three abstracts.

In general, the modelling methodology appears to draw on current approaches to evaluating cost-effectiveness of DMTs in RRMS. The authors used EDSS levels to define health states for CIS, with DMTs impacting on progression from CIS to RRMS. Once individuals progressed to RRMS, their disease progression was modelled using increasing EDSS scores and progression to SPMS. This seems a reasonable approach as EDSS levels were commonly used to describe populations recruited in clinical trials evaluating DMTs in CIS. In addition, it enables cost and utility data for RRMS patients to be utilised in the CIS model. For example, utility weights for

EDSS levels amongst CIS patients could be assumed to be equivalent to utility weights for comparable EDSS levels amongst RRMS patients.

The shorter time horizons some studies used to evaluate costs and consqeunces were of concern. As CIS patients progress to RRMS, and DMTs reduce this progression, it would seem important to incorporate the long-term costs and consquences of RRMS (either treatment with DMTs or best supportive care) in a cost-effectivness analysis of treatment strategies for patients with CIS.

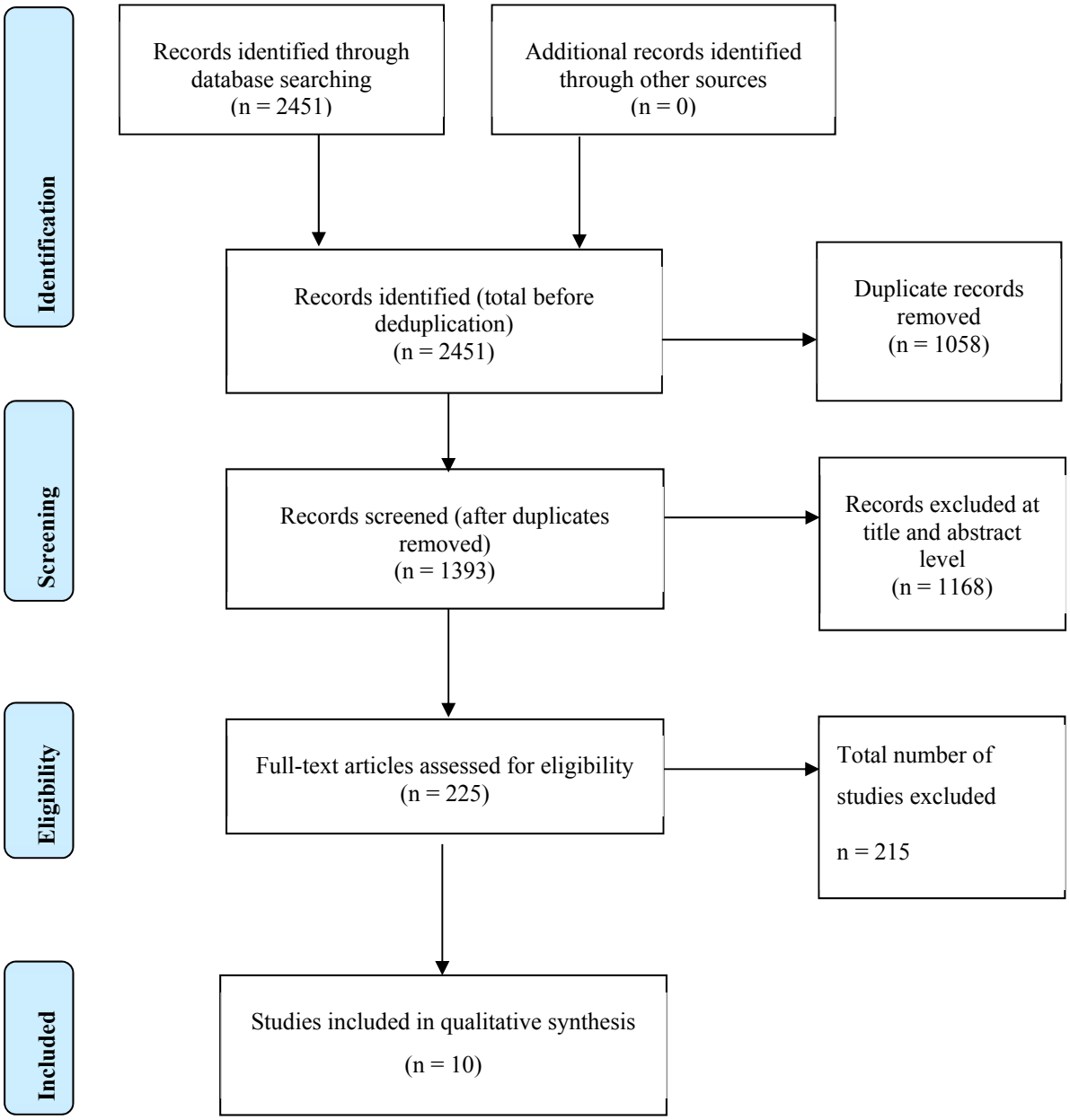
We appraised studies againgst the CHEERS and Philips' checklists on best practices for reporting economic evaluation and economic modelling studies. Based on our appraisal, the majority of the full text articles scored well in terms of defining the decision problem, outlining the study perspective, listing the intervention and comparators, presenting an illustrative model structure and providing a clear outline of the assumptions. Abstracts were limited in the amount of information that could be provided. From our review, we have raised some limitations/concerns, which mainly relate to the information required to populate the economic models. First, it was unclear on how authors made choices between data sources, especially utility values. It was unclear if utility values had been obtained from undertaking a systematic review. The, majority of the studies reporting their results in terms of QALYs provided references for these utility values. However, authors did not provide details on the descriptive tools/measure used to measure health-related quality of life, and also insufficient information is provided on who (CIS/MS patient or public) valued these health states. Second, the study undertaken by Zarco and colleagues[247] estimated treatment effect on conversion to MS from a number of trials. However, little information is provided on how a point estimate for the treatment effect was derived. Third, only two studies[239, 246] provided sufficient information on extrapolating the treatment effect beyond the trial time horizon. Finally, it was unclear if studies accounted for the uncertainty around extrapolating beyond the trail time horizon.

In Chapter 16, we have used information from this review to develop a de novo structure, which we used to estimate to cost-effectiveness of DMTs for treating people with clinically isolated syndrome.

12.4 *Results for the relapsing remitting multiple sclerosis studies*

The electronic database searches identified 2451 records (Figure 25). After removing duplicates, 1393 records were screened for inclusion. On the basis of title and abstract, 1168 records were excluded and the remaining 225 records were included for full-text screening. A further 215 articles were excluded at the full-text stage (see Appendix 7 for a list of excluded studies with reasons), leaving 10 studies[149, 248-256] that included a decision-analytical model used to estimate the cost-effectiveness of disease modifying treatments (DMTs) for treating people with relapsing-remitting multiple sclerosis (RRMS).

Figure 25: PRISMA flowchart for economic studies relating to RRMS



12.5 *Description of the included studies*

12.5.1 Summary of economic studies comparing DMTs for people with RRMS

***Sanchez-de la Rosa*[248]**

Sanchez-de la Rosa and colleagues (2012)[248] used a Markov model structure to assess the cost-effectiveness of IM IFN β-1a (Avonex), SC IFN β-1a 44mcg (Rebif), SC IFN β-1b (Betaferon) and SC GA (Copaxone) compared to symptomatic treatment for people in Spain diagnosed with RRMS. The model simulated the pathway for people with RRMS who received DMTs as compared to symptomatic treatment, and cost-

effectiveness was estimated over the model's time horizon. The model started with a hypothetical cohort of adults diagnosed with RRMS, and continued with people occupying/progressing to one of the following health states (EDSS 0.0-2.5, relapse EDSS 0.0-2.5, EDSS 3.0-5.5, relapse EDSS 3.0-5.5, EDSS 6.0-7.5, EDSS 8.0-9.5, and dead). Sanchez-de la Rosa and colleagues made a number of simplifying assumptions: people could die from natural causes in all health states except EDSS 8.0-9.5, all people in the model received symptomatic treatment for MS, people who discontinued treatment were assumed to receive symptom management alone, treatment reduced the amount of sick leave and people regardless of EDSS level were always working).

The model required information on the starting distribution by EDSS level, probability of progression, incidence of neutralizing antibodies, resource use and costs, and utility values by EDSS level. Information on utilities associated with RRMS were obtained from an observational study that was undertaken in Spain, which used a sample of people with MS who responded to the EQ-5D questionnaire. Resource use and costs, stratified by EDSS level, were obtained from published sources. Resource use and costs included pharmacological, MS management, and loss of productivity costs. The analysis was conducted from the Spanish societal perspective, and the results presented in terms of cost per life-years gained and costs per QALY gained over a 10-year time horizon. All costs were reported in Euros, 2010 prices. All costs and outcomes were discounted 3% per annum. Sanchez-de la Rosa undertook one-way sensitivity analysis (applied a 0% and 5% discount rates; varied time horizon to 2, 4, 6 or 8 years; changed the incidence of neutralizing antibodies and loss of productivity costs).

Base-case results in terms of cost per QALY showed that IM IFN β-1a was a dominant strategy when compared to SC IFN β-1b. However, treatment with IM IFN β-1a was not cost-effective when compared to SC GA at a willingness-to-pay threshold of €30,000 per QALY. Results from the sensitivity analyses demonstrated that the base-case results were robust and stable to changes made to model parameters.

Nikfar[249]

Nikfar et al.[249]estimated the cost-effectiveness of using symptom management in combination with IM IFN β-1a (Avonex), SC IFN β-1a (Rebif) or SC IFN β-1b (Betaferon/Extavia) compared with symptom management alone for the diagnosis of RRMS. The author developed a Markov structure to demonstrate the clinical pathway (RRMS defined by EDSS levels and transitioning to SPMS) that people would undergo for the treatment of RRMS. The model started with a hypothetical cohort of adults (30 years old) who received one of four treatment strategies. Some of the simplifying assumptions included people starting in EDSS 1-3.5. People could transition from RRMS to SPMS from the third cycle (approximately 5 years after diagnosis of RRMS, and it was assumed that this took place between EDSS 4-6 and EDSS 6-9.5). In case of withdrawal from IFNβ treatment in cycles 4 to 15, patients were allocated to the transition probabilities for relapse and disease progression used in the symptom management arm. Information required (probabilities of clinical events, and probabilities of switching to other IFN-β or symptomatic treatments and relapse rates) to populate the model was obtained from published sources through a literature review. Information on utility values, resource use and costs was obtained from a cross-sectional study undertaken by the authors. Briefly, 200 MS patients were recruited randomly from three referral hospitals of two cities, three private offices of MS specialists and members of the MS Iranian society. Authors elicited utility values directly from participants using the visual analogue scale, EQ-5D and Health Utility Index 3 (HUI-3) by in-house translated and validated questionnaires. Information on resource use and

costs was obtained using a retrospective approach in which information was collected at a single time point and covered the one-year period before inclusion in to the study. All prices were extracted from official tariffs, and reported in US dollars, 2012 prices. The analysis was conducted from the Iranian societal perspective and the base case results were expressed as an ICER based on the outcome of cost per QALY gained. All costs and outcomes were discounted at 7.2% per annum and 3% per annum, respectively. Base case results showed that when using the World Health Organization's recommendation on WTP thresholds (for developing countries, an ICER of less than three times the national GDP is considered cost-effective), all interventions except IM IFNβ-1a (Avonex) were cost-effective when compared to symptom management alone. However, using utility values based on EQ-5D, IM IFNβ-1a (Avonex) was shown to be cost-effective. Results from the sensitivity analyses showed that these results were robust except when changes were made to the use of copied biopharmaceuticals (CBPs) and biosimilars where these interventions were shown to be dominant.

Agashivala and Kim[250]

Agashivala and Kim (2012)[250] undertook a cost-effectiveness analysis using a decision tree. They simulated the costs and benefits of fingolimod or IFN-β for the first year and fingolimod in the second year as was done in the extension of the TRANSFORMS trial. They do not provide a description or diagrammatic representation of their model. They estimated costs of providing both treatments over the two years and compared these to the observed rates of relapse from the TRANSFORMS trial, and thereby estimated the additional costs per relapse avoided. Their definition of relapse, which was based on the definition used in the TRANSFORMS trial, was classified as new, worsening, or recurrent neurologic symptoms occurring 30 days from the onset of a preceding relapse and lasting for at least 24 hours without fever or infection. Relapses were confirmed if they were accompanied by an increase of at least one-half point on the EDSS, 1 point on 2 different functional systems of the EDSS, or 2 points on 1 of the functional systems (bowel, bladder, or cerebral functional systems were excluded). Resource use data were extracted from the literature and unit costs were obtained from the US 2010 Physician's Fee and Coding Guide. The costs were estimated from a US private payer perspective (health insurance), and included drug acquisition costs, and costs of monitoring and relapses. The analysis was undertaken over a time horizon of two years. Costs were adjusted to 2011 US Dollars, and future costs and outcomes were not discounted. The authors undertook one-way sensitivity analysis by varying input parameters by +/- 10%.

The estimated cost per relapse avoided was lower when fingolimod was started as first line treatment, than when it was started in the second year. They estimated the cost per relapse avoided to be $20,499 more in the delayed fingolimod group than in the early fingolimod group. Their findings are limited by the scope of the analysis undertaken. Their analysis does not take into account (or is not described) potential differences between the two treatments in terms of long-term health and cost impact, impact on disability/QoL, or consequences of adverse reactions to treatment. In addition, their parameter for risk of relapse was derived from a single clinical trial with inclusion and exclusion criteria that may limit generalisability to the general population. Their main findings are that it is more cost-effective to start fingolimod than to start IFN-β and then switch to fingolimod after one year of treatment. The findings have limited generalisability.

***Palace*[149]**

Palace and colleagues (Palace et al., 2015) developed a Markov model to simulate the long-term experience of people with RRMS. To model the natural history of RRMS, information from a baseline cohort was obtained from the British Columbia multiple sclerosis database. The clinical course of RRMS was modelled using health states which captured the long-term disability progression. Health states in RRMS were defined by EDSS levels 0-10. People who progressed to EDSS ≥ 6 were assumed to have converted to secondary progressive multiple sclerosis. From all health states people were subjected to risk of all-cause mortality or multiple sclerosis-related mortality. The treatment effect of DMTs (IFN-β or GA) on disability progression and relapse rates was obtained from the risk sharing scheme RSS Year 6 analysis. Transitions for both the treated and untreated cohorts occurred annually. In each model cyle, people incurred costs and accrued benefits based on the health state they occupied. Resource use and costs incurred were related to drug acquisition costs, cost for management by EDSS level and cost of relapse. Benefits accrued were measured in terms of health-related quality of life, and this information was obtained from a published sources.

Palace et al. (Palace et al., 2015) projected the cost-effectiveness of DMTs included in the RSS over a 20-year time horizon. The analysis was conducted from the UK NHS perspective, and the results presented in terms of an ICER and expressed as cost per QALY gained. All costs were reported in UK pounds and 2014 prices. All costs and benefits were discounted at 3.5% per annum. Authors undertook sensitivity analysis to determine if the base case results were sensitive to the choice of the natural history cohort.

***Pan*[251]**

Pan and colleagues used a Markov model and estimated the cost-effectiveness of IFN β-1b 250 µg (Betaferon/Extavia) compared to no treatment for people with RRMS. The model simulated the pathway for two cohorts (intervention versus no treatment) and cost-effectiveness was estimated over a 70-year time horizon. The model started with a hypothetical cohort of people who were ≥18 years old with clinically definite or laboratory–supported definite multiple sclerosis for >1 year, and who were ambulatory with EDSS ≥5.5, with at least two acute relapses during the previous two years. In the Markov model structure, the authors considered seven health states (EDSS 0.0-1.5, EDSS 1.0-2.5, EDSS 3-3.5, EDSS 4-5.5, EDSS 6-7.5, EDSS 8-9.5 and dead). In the model, people remained or progressed to more severe RRMS health states over six-monthly cycles. To have a workable model structure, the following assumptions were made: people who received mixed treatments during the post-trial period were assumed to have the same treatment efficacy as those who received IFNβ-1b during the trial period, a utility decrement of 0.0235 was applied to people who relapsed and this was assumed to last for six months, the model assumed no backward/regressive transitions, i.e. MS was seen as a progressive disease, the effectiveness of treatment was assumed to last for the duration of treatment, people who discontinued treatment were assumed to progress at the same rate as people in a natural history cohort, the model assumed that people with RRMS (EDSS <6.0) received treatment, and people who discontinued treatment were assumed not to re-initiate treatment.

Data required to populate the model were obtained from published sources. Clinical information on the risk of EDSS progression and relapse rates were based on a meta-analysis undertaken by the authors. Information on

utility values was obtained from a published source, and these were derived based on the EQ-5D. Utility values were allocated according to EDSS health state. Utility decrements were applied to people who relapsed independent of EDSS state. No disutilities for carers were included in the analysis. Resource use and costs stratified by EDSS level included were obtained from published sources. Resource use and costs included drug treatment costs, health state costs stratified by EDSS state, informal care costs and indirect (loss of productivity costs) costs. Authors applied a 10% discount to drug prices for IFN β-1b and mixed DMTs. The analysis was conducted from the USA societal perspective, and the results presented in terms of an ICER and expressed as cost per QALY gained. All costs were reported in USA dollars and 2011 prices. All costs and outcomes were discounted at 3% per annum. Pan and colleagues undertook one-way sensitivity analyses on key model input parameters (changing the time horizon, exclusion of productivity losses due to premature deaths, discount rate, and starting EDSS distribution) but did not undertake probabilistic sensitivity analysis.

The base case results in terms of life years gained showed that the discounted mean incremental gain was approximately US$86,200 with a reduction in life years loss of 2.8 year, which equated to an ICER of approximately US$31,000 per LYG. Results in terms of QALYs gained showed that the discounted mean incremental gain was approximately US$86,200 with a 1.9 years increase in quality–adjusted life years, which equated to an ICER of approximately US46,400 per QALY gained. Changes made to treatment discontinuation rate together with discounting on DMT drug costs resulted in moderate changes to the incremental cost effectiveness ratio. However, changes made to the time horizon (from 70 years to 20 years) resulted in the ICER (approximately US$163,600) becoming less cost-effective. Additionally, changing the starting distribution to 50% in EDSS 0.0-1.5 and 50% EDSS 2.0-2.5, resulted in a more cost-effective ICER of approximately US$19,600.

***Darba*[252]**

Darba et al undertook a cost-effectiveness analysis and compared the costs and consequences of treating RRMS with GA, IM IFN β-1a (Avonex), and combination therapy with GA and IFN. They undertook the analysis from the Spanish payer perspective, discounted future costs and outcomes, and adjusted costs to 2013 Euros. They built a Markov model with five health states relating to outcomes observed in the CombiRx RCT and estimated the incremental costs per relapses avoided. The model was run over 10 years with one-year cycle length. Transition probabilities were derived from the CombiRx RCT, whilst healthcare resource-use was obtained from other published sources. They assume the risk of exacerbation/relapses decreased over time (for the years after the end of the RCT). They undertook one-way and probabilistic sensitivity analysis.

Their main finding was that treatment with GA monotherapy dominated (less costly and fewer relapses) the other treatment options. They did not take into account the costs associated with adverse events, and it is unclear what the health state 'information lost' represents. It is likely it represents drop out from the main trial. These two issues may impact on the findings. The findings have limited generalisability as no other DMTs were considered, and disability and quality of life were not included in the model.

***Imani and Golestani*[253]**

Imani and Golestani undertook a cost-effectiveness analysis to estimate the incremental costs and benefits of four DMTs in comparison to best supportive care in Iran. They used a Markov model structure, and estimated costs and consequences over a lifetime horizon and from the Iranian societal perspective. Costs were estimated in 2011 US Dollars, and discount rates used reflect Iranian policy. Direct health provider costs included cost of treatment, monthly costs associated with EDSS states and cost of relapses. They are unclear as to whether they included other medical costs, for example costs of adverse drug events. Indirect costs included loss in productivity from absenteeism. In their model, nearly 75% of those modelled started with some degree of disability (EDSS score>2.5). In addition, they use fewer health states, noted by EDSS score, to model disability progression and to assign costs/utilities to, however, they provide no diagrammatic representation of their model.

They found that of the DMTs, treatment with IFN β-1a (Avonex) was the most cost-effective option. However, the ICER of IFN β-1a in comparison to best supportive care was 2011 US$607,397/QALY gained at the societal level. Their one-way sensitivity analysis found that the ICER was higher when analysis was undertaken over a shorter time horizon. The findings have limited generalizability due to the analysis setting, as resource-use reflects care and costs for Iran.

***Dembek*[254]**

Dembek et al[254] undertook a cost-effectiveness analysis to estimate the incremental costs and benefits of injectable DMTs in comparison to best supportive care in Spain. They compared three different regimens of IFN and glatiramer acetate (GA). They used a Markov model structure, and estimated costs and consequences over a 30 year time horizon and from the Spanish societal perspective. Costs were estimated in 2010 Euros. Direct health provider costs included cost of treatment, monitoring, adverse events and relapses. Indirect costs included loss in productivity from absenteeism and early retirement. They also included other non-medical costs (e.g. walking aids; informal care; and transportation). In their model, they assumed most MS patients start DMTs early, with minimal or no disability, and stop once EDSS score progresses to 6.0. In addition, they used fewer health states by EDSS score to model disability progression and to assign costs/utilities to, and assumed no additional mortality risk from MS.

They found that of the DMTs, treatment with IM IFNβ-1a (Avonex) was more cost-effective than SC IFNβ-1a 44 µg (Rebif), IFN β-1b (Betaferon/Extavia) or GA. The PSA showed that IM IFN β-1a was most cost-effective in 79-97% of simulations. However, the ICER of IM IFN β-1a in comparison to best supportive care was €168,629/QALY gained at the societal level. Their one-way sensitivity analysis found the findings were sensitive to DMT costs, cycle utilities, and disutility weights assigned to relapse events. They discuss their findings in relation to previous economic analysis but do not discuss the policy implications of the high ICER for DMT in comparison to best supportive. Their findings are also limited by not presenting findings from the health payer perspective as well.

Chevalier[255]

Chevalier et al[255] undertook a cost-effectiveness analysis to estimate the incremental costs and benefits of other DMTs in comparison to delayed-release dimethyl fumarate (DMF). They compared DMF to three different dosing regimens of IFN and three other DMTs. They used the same model structure as in previous NICE HTA of DMTs in MS, and estimated the cost-effectiveness from the French societal and payer perspectives. The model was run over 30 years with one-year cycle length and followed French guidelines for discounting. Costs were estimated in 2013 Euros, although the costs of drugs were for 2015. Direct health provider costs included the cost of drugs, monitoring, adverse events and management costs associated with EDSS health states and for relapses. Indirect costs included loss in productivity from absenteeism and early retirement.

They found that in comparison to DMF, glatiramer acetate, IFN β-1a 30 µg (Avonex), IFN β-1b 250 µg (Betaferon/Extavia), fingolimod and teriflunomide were dominated (i.e., higher costs and lower QALYs) by IFN β-1a 44 µg (Rebif) and DMF at both the societal and health payer perspective. The ICER for IFN β-1a 44 µg, in comparison to DMF, was €29,047/QALY and €13,110/QALY from the health payer and societal perspectives, respectively. The PSA found that at a WTP threshold of €30,000, the probability DMF was the most cost-effective option was 0.65. The one-way sensitivity analysis suggests that under the majority of scenarios they investigated, DMF continued to dominate other DMTs except IFN β-1a 44 µg. The found the ICER was most influenced by DMF disability progression rate, DMF acquisition cost, EDSS state cost and DMF relapse rate. Their main findings were that DMF is the optimal choice of DMTs.

Lee[256]

Lee et al.[256] undertook a cost-effectiveness analysis to estimate the incremental costs and benefits of fingolimod in comparison to IM IFN β-1a (Avonex). They estimated the cost-effectiveness from the USA societal perspective. The model was run over 10 years, with one-year cycle length and followed USA guidelines for discounting, with costs adjusted 2011 US Dollars. The model simulated costs and outcomes for hypothetical MS patients aged 37 years with minimal or no disability (EDSS score<2.5). Health states in the model reflected current EDSS score and whether the patient was on treatment. They assumed relapses lasted only for one month, and graded the severity of relapse, and assumed treatment was stopped once EDSS score>5.5. The direct health provider costs included the cost of drugs, monitoring and management costs associated with EDSS health states and for relapses. Indirect costs included loss in productivity from absenteeism, but it was unclear if this also included costs of early retirement. Quality of life weights were derived from US based studies.

They found that in comparison to intramuscular IFN β-1a 30 µg once weekly (Avonex), the ICER for treatment with fingolimod was US$73,975 per QALY gained from the societal level. The ICER was higher from the health payer perspective (US$81,794/QALY). The probabilistic sensitivity analysis found that fingolimod was not cost-effective at a willingness-to-pay (WTP) threshold of US50,000/QALY, but would be cost-effective if the cost of the drug were to drop.

Table 22: Characteristics of included economic evaluations in RRMS

Author, year and country	Attributes										
	Population	**Intervention and comparator**	**Perspective**	**Model type and cycle length**	**Health states**	**Time horizon**	**Evidence synthesis**	**Outcomes**	**Source of preference data**	**Discount rate**	**Sensitivity analysis**
Sanchez-de la Rosa et al., 2012[248] Spain	People with RRMS in Spain	IM IFN β-1a (Avonex); SC IFN β-1a (Rebif); SC IFN β-1b (Betaferon); SC glatiramer acetate (Copaxone) versus symptomatic treatment	Spanish societal perspective	Markov model with one month cycle lengths	Relapse EDSS 0.0-2.5, Relapse EDSS 3.0-5.5, EDSS 0.0-2.5, EDSS 3.0-5.5, EDSS 6.0-7.5, EDSS 8.0-9.5, and dead	10 years	Clinical information on disease progression and relapses obtained from a published study	Relapse rate estimation, disease progression estimation for EDSS 0.0-2.5 to EDSS 3.0-5.5 and disease progression estimation for EDSS 3.0-5.5 to EDSS 6.0-7.5	Utility values obtained from observational study undertaken in Spain, based on participant with MS who completed an EQ-5D questionnaire	3% per annum for both health outcomes and costs 7.5% for drug costs	Discount rate was set to 0% and 5%, the incidence of neutralizing antibiotics appearance, time horizon was set to 2,4,6 and 8 years
Nikfar, 2013[249] Iran	People with RRMS	Symptom management in combination with IM IFN β-1a, SC IFN β-1a or SC IFN β-1b compared to symptom management alone	Iranian societal perspective	Markov model with biennial cycle lengths	RRMS (EDSS 1-3.5, EDSS 4-6, EDSS 6.5-9.5), SPMS (EDSS 6.5-9.5), withdrawal, switching, Dead	30 years	Treatment effects were obtained from randomised controlled trials and long term follow-up studies	Number of people remaining in the RRMS state, number of people remaining relapse free, QALYs gained, total costs and productivity losses	Directly elicited from people with MS using the VAS, EQ-5D and HUI-3 instruments	7.2% per annum for costs and 3% for outcomes	Authors assessed the impact of using copied biosimilars and biosimilars in the analysis, using different sources of utility estimates, and sensitivity of discounting costs and outcomes
Agashivala and Kim 2012[250]	People with RRMS who had	Two years of fingolimod therapy versus IFN β-1a for one	United States of America commercial	Decision tree	No clear description or diagram with	Two years	Clinical evidence from the	Relapses avoided	Not applicable	Not reported	Univariate sensitivity

Author, year and country	Attributes										
	Population	**Intervention and comparator**	**Perspective**	**Model type and cycle length**	**Health states**	**Time horizon**	**Evidence synthesis**	**Outcomes**	**Source of preference data**	**Discount rate**	**Sensitivity analysis**
USA	experienced at least one documented relapse in the last two years	year followed by one year of fingolimod therapy	health plan (private insurance perspective)		the modelling approach reported		TRANSFORMS clinical trial				analyses undertaken
Palace, , 2015[149] UK	RRMS, ≥ 18 years, two clinically significant relapses in the previous two years, and EDSS level ≤5.5, and for SPMS, ambulant with relapses as the main driver of advancing disability	IFN β or glatiramer acetate	NHS and PSS perspective	Markov model with annual cycle lengths		20 years	Clinical information from RSS	Loss of utility (primary outcome) EDSS progression (secondary outcome)	Health-related quality of life information was collected from the EQ-5D questionnaire	3.5% per annum for both health outcomes and costs	Scenario analyses around discontinuation of DMTs, loss to follow-up, inclusion of SPMS at baseline, using information up to four years from the RSS, and changing the natural history cohort
Pan, 2012[251] USA	People age ≥18 years with clinically definite or laboratory – supported definite MS >1 year, are ambulatory with EDSS ≥5.5, and have had at least two acute relapses during the previous two years	IFN β-1b (250 µg) compared with no treatment	Societal perspective	Markov model with six month cycle length	EDSS 0.0-1.5, EDSS 1.0-2.5, EDSS 3-3.5, EDSS 4-5.5, EDSS 6-7.5, EDSS 8-9.5 and death	70 years	Authors have stated that risk of EDSS progression and relapse rates were obtained from published sources	Life years gained and quality-adjusted life years (QALYs) gained	Utility values obtained from a published source and these were based on information collected on EQ-5D	3% per annum applied to costs and outcomes	one-way sensitivity analyses: changing the time horizon, exclusion of productivity losses due to premature deaths, discount rate, and starting EDSS distribution

Author, year and country	Attributes										
	Population	**Intervention and comparator**	**Perspective**	**Model type and cycle length**	**Health states**	**Time horizon**	**Evidence synthesis**	**Outcomes**	**Source of preference data**	**Discount rate**	**Sensitivity analysis**
Darba, 2014[252] Spain	Spanish patients aged 18-60 with established RRMS. EDSS score 0-5.5 and who had experienced at least two exacerbations.	Combination Disease Modifying Treatments (GA and IFN β-1a)	Spanish National Health Service (NHS)	Markov model with annual cycle lengths	No relapses, suspected exacerbations, non- protocol defined exacerbations, protocol defined exacerbations, and information lost	10 years	Clinical evidence from the CombiRx clinical trial	Relapses avoided	Not applicable	3% per annum for both health outcomes and costs 7.5% for drug costs	Authors have undertaken one-way sensitivity analysis and probabilistic sensitivity analysis
Imani and Golestani, 2012[253] Iran	Multiple sclerosis patients in Iran	DMTs for MS (Avonex, Betaferon, Rebif and CinnoVex) versus symptom management/supportive care	Iranian MoH perspective, but costing perspective societal (incl. lost worker productivity)	Markov model	Four RRMS states determined by EDSS score (0-2.5; 3-5.5; 6-7.5; 8-9.5) Two relapsed states by EDSS score (0-2.5; 3-5.5) Death	Until death	Unclear	Time spent in EDSS 0.0-5.5, time spent relapse-free, life-years gained and QALYs gained	Published literature	3% per annum for both health outcomes and costs	Unclear on the type of SA (e.g. one way) undertaken
Dembek, 2014[254] Spain	MS patients aged 30 and with no or minimal disability (57 % with EDSS scores of 1–1.5 and 43 % with EDSS scores of 2–2.5)	IM IFN β-1a (30µg administered once weekly) SC IFN β-1a (44µg administered every other day) IFN β-1b (125 µg administered thrice weekly)	Societal	Markov model with annual cycle lengths	Four RRMS states determined by EDSS score (0-2.5; 3-5.5; 6-7.5; 8-9.5) Two relapsed states by EDSS score (0-2.5; 3-5.5)	30 years	Unclear	QALYs	Published literature	3% per annum for health outcomes and costs	Univariate sensitivity analysis and probabilistic sensitivity analysis

Author, year and country	Attributes										
	Population	**Intervention and comparator**	**Perspective**	**Model type and cycle length**	**Health states**	**Time horizon**	**Evidence synthesis**	**Outcomes**	**Source of preference data**	**Discount rate**	**Sensitivity analysis**
		GA (20 mg administered daily)			Death						
Chevalier, 2016[255] France	People with RRMS	IFN β-1a 44 µg dose IFN β-1a 30 µg dose IFN β-1b 250 µg dose GA teriflunomide; fingolimod versus delayed-release DMF	Health payee and societal perspectives	Markov model with annual cycle lengths	RRMS and SPMS health states	30 year	Information on risk of adverse events obtained from a systematic review undertaken by the authors	QALYs	EQ-5D responses from a study undertaken amongst MS patients in France, and utility scores derived using French tariff set	4% per annum for first 30 years then 2% thereafter	Probabilistic sensitivity analysis
Lee, 2012[256] USA	People with RRMS with a mean age of 37 years	Fingolimod 0.5mg orally once a day versus intramuscular IFN β-1a 30mcg once weekly	USA societal perspective	Markov model with annual cycle lengths	RRMS non-treatment states determined by EDSS score (0-2.5; 3-5.5; 6-7.5; 8-9.5) Two treatment states by EDSS level (0-2.5; 3-5.5) Temporary relapse health state Death	10 years	Unclear	QALYs	Unclear	3% per annum for both costs and outcomes	One-way and probabilistic sensitivity analysis

CDMS, clinically definite multiple sclerosis; CIS, clinically isolated syndrome; DMTs, disease modifying treatment; EDSS, expanded disability status scale; EQ-5D, euroQol five dimensions; HUI, health utility index; MoH, Ministry of Health; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SA, sensitivity analysis; SC, subcutaneous; VAS, visual analogue scale

12.6 *Summary of overall cost-effectiveness evidence*

The characteristics of the studies included in this review are presented in Table 22. All of the studies included an economic model to estimate the cost-effectiveness of using DMTs for treating people with RRMS. The economic evaluations were mainly conducted in the USA[250-252, 254, 256] and Spain.[248] Two studies[249, 253] were undertaken in Iran, and the remaining studies in the UK[149] and France.[255] Studies[248, 249, 253, 254] mainly compared IFN β-1a 30µg intramuscular injections once weekly (Avonex), IFN β-1a three-times weekly (Rebif), IFN β-1b subcutaneous (Betaferon) or glatiramer acetate (Copaxone) with symptom management. Two studies[149, 252] compared IFN β-1a 30 µg IM once weekly (Avonex) with glatiramer acetate, one study[251] compared IFN β-1b subcutaneous (Betaferon) with symptom management, the two studies[250, 256] included IFN β-1a 30 µg IM once weekly (Avonex) in their intervention compared to fingolimod. The remaining one study[255] included comparisons between IFN β-1a, IFN-β 1b, or glatiramer acetate with dimethyl fumerate.

All studies[248, 249, 251-256] except Agashivala and Kim 2012[250] used a Markov cohort model structure to determine the cost-effectiveness of DMTs for RRMS. Agashivala and Kim 2012[250]used a decision tree structure. For those studies[149, 248, 249, 251-256] using a Markov model structure, model cycle lengths were one month[248], six months[251], annual[149, 252-256], or biennial[249] and time horizons ranged from two years[250] up to to death[253]. Five studies[248, 249, 251, 254, 256] analysed from the societal perspective alone, two studies[149, 252] from the national health service perspective, two studies[253, 255] from both a health service and the societal perspectives, and one study[250] from the third-party provider persepctive. Six studies[248, 251-254, 256] used a discount rate of 3% per annum for costs and outcomes, one study[255] applied an annual 4% discount rate for costs and outcomes, one study[149] applied a 3.5% annual discount rate, one study[249] used a discount rate of 7.2% for costs and 3% for outcomes, and the final study[250] did not explicitly state the discounting approach. Additionally, two studies[248, 252] included a discount rate of 7.5% for cost of drugs. Results were mainly presented in terms of relapses avoided, life years gained and QALYs.

12.6.1 Definition of relapsing remitting multiple sclerosis

The definitions used to characterise people with relapsing remitting multiple sclerosis were consistent across all studies. However, to our knowledge no studies elaborated on the definitions used to define multiple sclerosis from the clinical studies that were used to obtain treatment effects of disease modifying treatments.

12.6.2 Characteristics of relapsing remitting multiple sclerosis

All studies considered disease progression based on the use of EDSS to capture disability progression in people with RRMS. All models also captured the relapsing nature of MS. Nine studies[248-256] grouped EDSS health states (e.g. EDSS 1-3.5[249]) but authors did not provide justification on how these groupings were derived. In contrast, Palace and colleagues[149] modelled each EDSS level to show disease progression. One study[249] clearly presented definitions for each health state included in their model. Three studies[149, 249, 256] included the conversion of relapsing remitting multiple sclerosis to secondary progressive MS. Only one study[149] allowed for people to transition to less severe health states. In studies[149, 249, 256] that considered relapses in their models,

authors assumed that relapses occurred up to EDSS 5.5. At this level, authors assumed that people discontinued treatment and followed the same pathway as people who were at the same EDSS level but untreated.

In general the risk of death was obtained from country-specific lifetime tables for the general population. Two studies[248, 256] assumed that people were at risk of MS-related death at EDSS 8-9.5. However, it was unclear if Sanchez-de la Rosa et al.[248] varied the risk of death by age. Nikfar and colleagues[249] used another method to account for death. These authors assumed that multiple sclerosis increased the risk of death by threefold across age and sex adjusted mortality rates. Pan et al. modelled mortality based on extrapolating survival data from an observational study. These authors fitted a Weibull parametric model to the placebo (no treatment) group, then adjusted by using estimates on a hazard ratio derived from a comparison between treatment and a placebo group. Evidence on other parametric model fits were not presented by the authors.

12.6.3 Treatment effect of disease modifying treatment in relapsing remitting multiple sclerosis

The effect of treatment on disability progression and frequency of relapses was considered in all studies by applying a hazard ratio/relative risk to a baseline cohort of people with RRMS. All studies drew on the evidence from randomized controlled trials. However, only one study[248] was clear on the meta-analytical methods used to estimate the treatment from clinical trials. These authors used log-linear regression in order to estimate the treatment effect of disease modifying treatment on disease progression and relapse frequency.

It was unclear if studies modelled the direct impact of DMTs in the conversion to secondary progressive multiple sclerosis. All studies considered an indirect impact of disease modifying treatments on mortality by showing that disease modifying treatments delays disease progression.

It was not clear whether any studies accounted for the waning effect of disease modifying treatment. One study[248] considered the effect of neutralising antibodies on the efficacy of disease modifying treatments.

12.6.4 Discontinuation of treatment in relapsing remitting multiple sclerosis

Discontinuation rates were considered in all [149, 248-256] analyses except the study undertaken by Agashivala and Kim [250]. Treatment discontinuation was assumed to be a result of adverse events from drug utilisation, and/or progressing to EDSS ≥6 or perceived lack of efficacy[249]. To our knowledge, no studies fitted a parametric model to long-term data in order to derive time dependent transition probabilities for people discontinuing treatment. Studies used short-term information on discontinuation rates from trials and assumed a constant hazard over time for the duration of the model.

12.7 *Quality assessment*

We present a summary of the reporting quality of the studies included in the current review assessed against the Philips et al.[229], which covers model structure, information required for the model, and uncertainty. Details of the quality assessment of each study are presented in Appendix 7.

12.7.1 Model structures

Structures of the models included in this review were generally of satisfactory quality. In accordance with best practice for developing model structures, studies clearly stated their respective decision problems and the viewpoint/perspective of the analysis, and the objectives of the model, all of which were consistent with the decision problem. Additionally, illustrative structures captured the relapsing nature of multiple sclerosis and followed the pathway for people treated for RRMS. Whilst good reporting quality was noted in most studies, there were some structural issues noticed. These related to the time horizon, the model structure, half-cycle corrections, and the generalisability of the results. In four studies[149, 248, 250, 256], the time horizon was possibly too short to capture all costs and benefits of treatment with DMTs. Agashivala and Kim (2012)[250] used a decision tree structure and affixed probability estimates for progression at discrete/fixed timepoints. As a result, this does not reflect the true nature of RRMS. A Markov model would have been more appropriate because of the chronic nature of the disease and the long time horizons for progressing to more severe EDSS levels. Additionally, the health states included in the model structure were not clearly described. One study[248] used a one-month cycle length in their model, but this does not reflect the routine follow-up for people with RRMS; an annual cycle length would have been more appropriate. On the other hand, Nikfar and colleagues used a model cycle over two years, although it was unclear if these authors used a half-cycle correction.

In general, all studies[149, 248-256] stated the location of the analyses but not the settings, which prevents assessment of the generalisability of the results.

12.7.2 Information required

The methods used to identify relevant information to populate the models were satisfactory in most studies[248-250, 252, 254-256]. All studies provided references for their model inputs but quality appraisal and selection of relevant inputs was rarely made transparent. In all studies [149, 248-256], information was required on the treatment effect of DMTs on progression and relapse rates, resource use and costs, outcomes and mortality.

The effects of treatment with DMTs on disease progression compared to no treatment were modelled using hazard ratios. The relative reduction in disability progression associated with DMTs was applied to the predicted baseline cohort of people with RRMS. In some analyses, studies obtained this hazard ratio directly from a trial or have obtained this hazard ratio through reviewing the clinical effectiveness literature. However, studies that used the latter approach did not elaborate on the quality assessment of these RCTs or provide sufficient detail on how the hazard ratio had been derived. Information on a baseline chort of people could be obtained from MS registries, natural history cohort or from a placebo arm of a trial. In all studies, information on disease progression in a baseline cohort were obtained from RCTs. All models considered the treatment effect on a reduction in relapses. The treatment effect on the average number of relapses experienced by EDSS level, was obtained from published sources. Most studies undertook analyses based on a long time horizon, which is in line with the NICE reference case. However, authors have not elaborated on the techniques used to extrapolate the treatment effects beyond the time horizon of the RCTs. Studies using a shorter time horizon, for example Lee et al. (2012)[256], did not assume treatment benefit beyond the length of the follow-up study.

Information on resource use and costs was obtained from published sources, and these were well documented in some studies. Details of resource use, by EDSS level were well documented in the study undertaken by Nikfar and colleagues[249].

12.7.3 Uncertainty

All studies included one-way sensitivity analysis, undertaken by changing key model inputs to determine the robustness of their base case results. In sensitivity analyses authors made changes to discount rates, time horizon, initial EDSS distribution of people in the starting cohort, perspective of the analysis, discontinuation rate, and utility values. To our knowledge, authors did not use information from a natural history cohort of people to model disease progression as part of their sensitivity analyses, or allowed for waning treatment effect over time.

12.8 *Summary of the RRMS cost-effectiveness evidence*

We identified 10 recent studies[149, 248-256] that used an economic model to estimate the cost-effectiveness of disease modifying treatment for treating people with relapsing remitting multiple sclerosis. The evidence offers insight on the modelling methodology, which includes the illustrative structures to depict multiple sclerosis progression, key model inputs, and assumptions made in order to assess the cost-effectiveness. These methods appear to be feasible across all studies.

We appraised studies against the CHEERS[228] and Philips'[229]) checklists on best practices for reporting economic evaluation and economic modelling studies. Based on our appraisal, studies performed well against these checklists in terms of reporting sufficient information on the decision problem, outlining the study perspective, listing the intervention and comparators, presenting an illustrative model structure and providing a clear outline of the assumptions. Our review highlights some limitations of the studies, and these are related to the structure and the information required to populate. In terms of the structure, the time horizon was short in some studies, and the choice of model structure did not accurately reflect or capture the disability progression associated with multiple sclerosis. Limitations associated with model information relate to the lack of detail on quality assessment of clinical effectiveness studies and lack of detail on the methods used to meta-analyse information from clinical studies, and insufficient information on extrapolating treatment effect beyond trial time horizons. Additionally, we noted some limitations in the methods used to model mortality.

In Chapter 15, we draw on the information from this review in terms of model design and model inputs, to estimate the cost-effectiveness of disease modifying treatments for treating people with RRMS.

13 RISK SHARING SCHEME SUBMISSION

13.1 *Overview of Risk Sharing Scheme model*

In the RSS model, an economic analysis was conducted to assess the cost-effectiveness of the combined treatment effect of disease modifying treatments, IFN β-1a 44 or 22 µg SC thrice weekly (Rebif), GA 20 mg SC daily (Copaxone), IFN β-1b 250 µg SC every other day (Betaferon) and IFN β-1a 30 µg IM weekly (Avonex) included in the Risk Sharing Scheme (RSS) compared with best supportive care for people with relapsing-remitting multiple sclerosis.[149]

In the analysis, a Markov model was used to depict the natural history of people with RRMS, including progression to secondary progressive multiple sclerosis (SPMS). Information required on the natural history of people with RRMS was based on the British Columbia multiple sclerosis (BCMS) cohort. Two sets of transition probabilities were reported: transitions based on the age of onset of RRMS below (subgroup 1) and above (subgroup 2) the median age. In both the natural history and RSS cohorts, disability progression was characterized by using the Expanded Disability Status Scale (EDSS), which ranges from 0 to 10 (Death). In addition to progressing to more severe EDSS states, people were allowed to regress to less severe EDSS states, which reflected the natural course of the disease. In the model, only people in EDSS state 7-9 could progress to EDSS 10 (death). Additionally, it was assumed that the standardized mortality rate increased by two-fold, regardless of the age of onset or severity of MS.

In the treatment arm (RSS model), it was assumed that each year 5% of people would discontinue DMTs, and that this might be due to adverse events or progression to EDSS 7-9. It was assumed that people who discontinued treatment would remain off treatment for the remainder of their life.

The analysis was undertaken from the UK NHS perspective in a primary care setting. Health outcomes were measured in quality-adjusted life-years, and the analysis was undertaken over a 50-year time horizon. Information on utilities by EDSS state were obtained from pooling utility estimates from the 2002 and 2005 MS Trust surveys, based on information collected on the EQ-5D, which was subsequently converted to an EQ-5D index score. Information on resource use and unit costs was obtained from the ScHARR[257] report and subsequently inflated to current prices. The results were presented as an ICER and expressed as cost per QALYs gained. Both costs and benefits were discounted at 3.5% per annum.

Base case results showed that for people in subgroup 1, mean cost per person in the treatment arm was approximately £357,100 with a mean of 7.987 QALYs gained per person. For best supportive care, the mean cost per person was approximately £328,800 with a mean of 6.947 QALYs per person. Consequently the incremental cost-effectiveness ratio (ICER) was approximately £27,200 per QALY. In subgroup 2, the mean cost per person in the treatment arm was approximately £379,300 with 8.022 QALYs gained compared to the best supportive care arm of approximately £355,500 with 7.028 QALYs gained. This gave an incremental cost-effectiveness ratio (ICER) of approximately £23,900 per QALY. Overall, the mean incremental cost of DMTs compared to best supportive care was approximately £25,600 with a corresponding 1.013 QALYs gained, and an ICER of approximately £25,300 per QALY.

A number of sensitivity analyses were undertaken:

1. Excluding EDSS scores for people who switched to a non-scheme DMT from the analyses
2. Using imputation techniques for missing values in the multi-level model.
3. Changing the assumption made in the Markov model about the treatment effect of DMTs on backward transitions
4. Supplementing transition probabilities derived from the BCMS with imputed values

Results for sensitivity analysis 1 showed a marginal increase in treatment effect for the base run. For sensitivity analysis 2, slight differences were seen between treatment effects. No probabilistic sensitivity analyses were undertaken. Table 23 gives a summary of the RSS model.

Table 23: Summary of the RSS model

Parameter	Risk sharing scheme model
Natural history cohort	British Columbia cohort
Population	People initially diagnosed with RRMS and those who progress to SPMS
Intervention	Disease modifying treatments available in the RSS: • IFN β-1a 30 µg IM once a week (Avonex) • IFN β-1a 44 or 22 µg SC three times per week (Rebif) • IFN β-1b 250 µg SC every other day (Betaferon) • Glatiramer acetate 20 mg SC daily (Copaxone)
Comparator	Best supportive care
Type of model and health states	Markov model
Hazard ratio	Targeted outcomes were agreed on for each of the four DMTs included in the RSS, expressed as hazard ratios of disability progression for treated compared to no treatment
Resource use and costs	Disease modifying treatment costs, health state/EDSS costs and cost of relapses
Health-related quality of life	Utility values were pooled from the 2002 and 2005 MS Trust surveys
Discontinuation of treatment	Assumed that 5% people would discontinue treatment every year.
Relapse	Weighted average of the frequency of relapses for people with RRMS and SPMS, irrespective of EDDS level
Adverse events	Utility decrement of 0.02 associated with adverse events from disease modifying treatments. It was assumed that this decrement would only apply to the first year of commencing treatment
Mortality	MS-related death for people in EDSS 7-9. For all states, a standardised mortality rate estimated and multiplied by two to take into account MS-related and non-MS related mortality
Time horizon	50-year time horizon
Base-case analysis results	Using the 'base run' model, an ICER of approximately £25,300 per QALY was derived. Using the 'time-varying model', an ICER of approximately £33,700 per QALY was derived
Sensitivity analysis (and PSA) results	No PSA was undertaken
EDSS, expanded disability status scale; ICER, incremental cost-effectiveness ratio; MS, multiple sclerosis; NICE, National Institute for Health and Care Excellence; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-years; RRMS, relapsing-remitting multiple sclerosis; RSS, Risk Sharing Scheme; SPMS, secondary progressive multiple sclerosis	

13.1.1 Evidence used to parameterise the Risk Sharing Scheme (RSS) multiple sclerosis model

The model was populated with clinical information from the Risk Sharing Scheme and secondary sources. Information required to parameterise the model included evidence on the natural history of people with relapsing remitting multiple sclerosis, aggregate treatment effect of disease modifying treatments, adverse events, resource use and costs, mortality, and health-related quality of life.

13.1.2 Natural history of relapsing remitting multiple sclerosis

The natural history of RRMS and SPMS was estimated using the British Columbia multiple sclerosis (BCMS) database. Details of the BCMS cohort have been published elsewhere (Palace et al., 2014). In brief, the BCMS cohort is a population-based database established in the 1980s which captures about 80% of people with multiple sclerosis in British Columbia, Canada (Palace et al., 2015). EDSS scores were recorded by MS specialists after face-to-face consultation with patients, and this usually occurred at the annual visit to the MS clinic. In the database, people who progressed to secondary progressive multiple sclerosis were not censored. However, all patients were censored in 1996 as a result of the introduction of disease modifying treatments in British Columbia, Canada. This database is considered to be large (by 2004, the BCMS had over 5900 participants), with prospectively collected information (e.g. EDSS scores, relapses, adverse events) and a long term follow-up (>25,000 cumulative years), and the database covers a relatively recent time period[149].

13.1.3 EDSS progression in the British Columbia cohort

The 'method of Jackson'[258] was used to depict the natural history of MS, based on the observation of people with relapsing-remitting multiple sclerosis in the BCMS. Transition matrices were derived for people whose age of onset of MS was below and above the median age. Table 24 and Table 25 show the transition matrices derived for people whose age of onset of RRMS was below (subgroup 1) and above (subgroup 2) the median age, respectively. Disability progression was characterized using the EDSS. In addition to progressing to more severe EDSS states, people were allowed to improve to less severe EDSS states, which reflects the natural course of the disease. From the transition matrix, only people in EDSS state 7-9 could progress to EDSS 10 (MS-related death).

Table 24: Natural history transition matrix based on information from British Columbia multiple sclerosis database (below the medium)

		EDSS state										
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
EDSS state	**0**	0.6870	0.0612	0.0169	0.0062	0.0018	0.0005	0.0001	0.0000	0.0000	0.0000	0
	1	0.2110	0.6787	0.1265	0.0522	0.0225	0.0056	0.0014	0.0002	0.0000	0.0000	0
	2	0.0720	0.1664	0.5955	0.1165	0.0662	0.0291	0.0045	0.0005	0.0000	0.0000	0
	3	0.0224	0.0646	0.1729	0.5439	0.1210	0.0594	0.0252	0.0026	0.0003	0.0000	0
	4	0.0043	0.0170	0.0454	0.0945	0.4874	0.0915	0.0321	0.0073	0.0006	0.0000	0
	5	0.0014	0.0047	0.0184	0.0573	0.1009	0.4727	0.0424	0.0042	0.0005	0.0000	0
	6	0.0018	0.0067	0.0219	0.1148	0.1664	0.2810	0.7283	0.1220	0.0187	0.0014	0
	7	0.0001	0.0005	0.0018	0.0107	0.0262	0.0396	0.1151	0.6814	0.0570	0.0045	0
	8	0.0000	0.0001	0.0005	0.0037	0.0069	0.0191	0.0457	0.1628	0.8544	0.1301	0
	9	0.0000	0.0000	0.0000	0.0004	0.0007	0.0014	0.0052	0.0189	0.0608	0.6252	0
	10	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001	0.0077	0.2387	1

Table 25: Natural history transition matrix based on information from British Columbia multiple sclerosis database (above the medium)

		EDSS state										
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
EDSS state	**0**	0.6954	0.0583	0.0159	0.0059	0.0017	0.0005	0.0001	0.0000	0.0000	0.0000	0
	1	0.2029	0.6950	0.1213	0.0496	0.0221	0.0053	0.0013	0.0001	0.0000	0.0000	0
	2	0.0725	0.1578	0.6079	0.1201	0.0666	0.0294	0.0044	0.0005	0.0000	0.0000	0
	3	0.0217	0.0609	0.1680	0.5442	0.1152	0.0587	0.0250	0.0025	0.0003	0.0000	0
	4	0.0042	0.0164	0.0446	0.0911	0.4894	0.0874	0.0307	0.0073	0.0005	0.0000	0
	5	0.0014	0.0046	0.0185	0.0584	0.1039	0.4869	0.0408	0.0038	0.0005	0.0000	0
	6	0.0018	0.0064	0.0216	0.1165	0.1681	0.2731	0.7407	0.1168	0.0187	0.0013	0
	7	0.0001	0.0005	0.0017	0.0103	0.0258	0.0388	0.1089	0.6926	0.0553	0.0043	0
	8	0.0000	0.0001	0.0005	0.0036	0.0067	0.0188	0.0438	0.1606	0.8964	0.1326	0
	9	0.0000	0.0000	0.0000	0.0003	0.0006	0.0010	0.0042	0.0156	0.0205	0.6230	0
	10	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001	0.0077	0.2387	1

13.1.4 Types of multiple sclerosis

The model includes people who commenced in a RRMS health state and who progressed to SPMS. People with clinically isolated syndrome, primary progressive multiple sclerosis or benign disease were not included in the RSS as treatment options included in the Scheme were not licensed for these types of multiple sclerosis (Tappenden et al., 2001).

13.1.5 Interventions

The RSS model compares the combined treatment effects of using IFN-β and glatiramer acetate compared to best supportive care for people with RRMS. Table 26 shows the drugs and dose regimes with their licensed indications in the UK. The Y10 analyses included people whose EDSS scores were recorded after they had switched to non-scheme DMTs. The assessment group was not clear on the non-scheme DMTs included in the RSS. Sensitivity analysis was conducted around the treatment effect, which was to censor people whose EDSS scores were recorded after switching treatment. Censoring these people resulted in an increase in the combined treatment effect (HR=0.7666).

Table 26: Interventions included in the RSS

Company	Drug	Dose regime	Route of administration	Licensed indications
Avonex	IFN β-1a	30 µg once a week	Intramuscular	RRMS
Rebif		RRMS: 44 µg three times per week (22 µg three times per week for patients who cannot tolerate the higher dose)	Subcutaneous	RRMS SPMS
Betaferon/Extavia	IFN β-1b	250 µg every other day		RRMS SPMS
Copaxone	Glatiramer acetate	20 mg once daily		RRMS
IFN, interferon; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis				

13.1.6 Population

The population included in the RSS model is similar to the population in the BCMS. In the RSS, the population was stratified by age of onset of RRMS and by EDSS score. The initial distribution of people in each EDSS state is presented in Table 27.

Table 27: Baseline distribution of people in the RSS

EDSS	Age of onset below median	Age of onset above median	Total
0	61	74	135
1	295	394	689
2	411	677	1088
3	401	569	970
4	273	379	652
5	162	279	441
6	76	166	242
7	0	0	0
8	0	0	0
9	0	0	0
10	0	0	0
Total	1679	2538	4217

13.1.7 Mortality rate

Two types of mortality were included in the economic model, MS-related death (EDSS 10), and death from other causes. General population mortality was obtained from the Office of National Statistics (ONS) 2010, and a weighted average was taken to represent the distribution of males and females in the economic model. People with RRMS and SPMS were assumed to have a higher mortality rate than those in the general population. It was assumed that the standardized mortality rate increased two-fold, regardless of the age of onset or severity of MS, and EDSS level. The assessment group noted that the same transition probabilities from EDSS 7-9 to MS-related death were used for both natural history subgroups and also for both active therapy subgroups. The assessment group were concerned that MS-related mortlity may have been overestimated, as individuals in the model also die as a result of progression to EDSS 10 (death).

13.1.8 Resource use and costs

All costs included in the analysis were those directly related to the NHS and PSS perspective, and were reported in UK pounds (£) sterling in 2015/16 prices. The RSS model included the following resource use and costs in order to conduct analyses:

1. Disease modifying treatment costs
2. Health state/EDSS costs
3. Cost of relapse

13.1.9 Disease modifying treatment costs

Table 26 shows the DMTs included in the RSS model. A weighted average of these treatments was taken and a mean cost of £7300 per year was derived for people who received treatment. Drug prices were agreed as part of the Risk Sharing Scheme. However, it was not clear how these weighted averages were derived.

13.1.10 Health state/EDSS costs

Information on resource use and costs associated with treating multiple sclerosis from a UK perspective were obtained from a cross-sectional observational study (Working Paper) undertaken by Kobelt and colleagues (Kobelt et al., 2000).[259] The Kobelt study obtained resource use information in order to derive costs of multiple sclerosis from a societal perspective (direct and indirect costs), but also provided disaggregated information relating to the direct costs (detection, treatment, rehabilitation and long-term care of illness). The direct costs included inpatient care, ambulatory care, social care, drug treatment, investments made to the home and informal care (care provided in the absence of family). The study reported that direct costs (including informal care) accounted for 54% of the total costs, and the remaining 46% represented indirect costs. However, excluding informal care from the analysis, direct costs accounted for 38% of the total costs per patient per year. The costs were estimated for each individual patient in the study, and an average cost per patient was reported with respect to the different levels of disability (mild, moderate, severe). All costs were reported in UK pounds (£) sterling at 1999/00 prices.

The previous report submitted by ScHARR[257] suggested that 244 out of the 622 records were excluded because respondents had primary progressive multiple sclerosis, benign multiple sclerosis or information on EDSS state was missing. Mean direct costs by EDSS state and mean cost of a relapse reported in the current submission were based on information supplied to the ScHARR team in confidence, and the assessment group did not have access to this information. Costs in the ScHARR submission were subsequently inflated to current prices (2015/16) using the appropriate indices from the Hospital and Community Health Services (HCHS) pay and price index 2015/16[260], and the assessment group believes that these have been appropriately derived. Table 28 shows the costs included in the model.

Despite these mean costs being correctly derived, the RSS report assumes that resource use and patient management have not changed since 1990/00. The assessment group believes that a systematic review could have been conducted to obtain more recent information on resource use.

The assessment group is unable to provide comment on:

1. The resource use information valued to derive mean unit costs per EDSS state
2. The number of people reporting on resource use in each health state
3. The percentage of people receiving each drug treatment
4. Distribution of resource use, and the techniques used to account for skewness of costs, if this existed
5. The techniques used to account for missing data, if this existed
6. ‘Mapping’ from mild, moderate, and severe disability onto the EDSS

Table 28: Mean unit costs included in the RSS model

EDSS state	Unit costs, £ 1999/00 prices	Unit costs, £ 2015/16 prices
0	756	1164
1	756	1164
2	756	1164
3	1394	2147
4	1444	2225
5	5090	7840
6	5678	8746
7	17, 327	26, 688
8	26, 903	41, 439
9	34, 201	52, 679
10	0	0

13.1.11 Cost of relapse

The cost of a relapse included in the RSS model was obtained from the ScHARR analysis[257], and subsequently inflated to current prices using the Hospital and Community Health Services (HCHS) pay and price index 2015/16[260]. The cost represents an average cost regardless of the severity of the relapse. The cost of a relapse was the same in the treatment and no treatment arms of the model. As with health state costings, the assessment group noted that the original cost year was 1999/00 and assumptions are made that resource use and management have not changed since the base year. Despite this assumption, the assessment group considers the cost of relapse (£4263) to have been derived correctly. However, the assessment group is unclear on the components/resources costed in order to derive this cost. Additionally, the assessment group believes that a review of the literature could have been undertaken to obtain more recent information.

The costs included in the model were related to drug treatment costs, health state/EDSS costs, and relapse costs. The assessment group was not clear if the cost of treating adverse events, administering the drugs or monitoring treatments were included in the analysis. For example IFN β-1a (Avonex) is administered intramuscularly, and would incur additional directs costs (e.g. training patients or carers to administer injections).

13.1.12 Health state utility values

The primary outcome measure used in the model was a 'deviation score of the average observed loss of utility.' Health outcomes were measured in QALYs, with utility weights assigned to the health states in the model. The utilites used in the RSS model were derived by first pooling values from two MS Trust surveys (2002 and 2005) and then substracting the carer's disutility. Utilities obtained from Boggild et al. as used in the ScHARR report[257] were derived based on information from a two-stage survey of 1554 respondents from the MS Trust database. To our understanding, these three sets formed the three-pooled dataset. Utility estimates, by EDSS, were derived based on information collected on the EQ-5D, which was subsequently converted to an EQ-5D

index score. Alternative utility values were derived based on pooled datasets from the ScHARR model, and also from the UK MS RSS cohort. Table 29 shows the utility values used in the RSS model.

Table 29: Mean utility values used in the model

EDSS state	Boggild dataset	Three-pooled dataset	Two-pooled dataset	Carer's disutility
0	0.7850	0.8722	0.9248	-0.002
1	0.7480	0.7590	0.7614	-0.002
2	0.6900	0.6811	0.6741	-0.002
3	0.5827	0.5731	0.5643	-0.002
4	0.5827	0.5731	0.5643	-0.045
5	0.5790	0.5040	0.4906	-0.142
6	0.4740	0.4576	0.4453	-0.167
7	0.3650	0.2825	0.2686	-0.063
8	0.2640	0.0380	0.0076	-0.095
9	-0.1770	-0.2246	-0.2304	-0.095
10	0	0	0	0

13.1.13 Carer's disutility

An analysis was undertaken which included carer's disutilities by EDSS state. Table 29 shows the disutility values used in the model. Initially, the assessment group was unclear on the source of these disutilities. However, on clarification the Department of Health suggested that these values were obtained from a study by Acaster and colleagues (2013).[261] The assessment group examined the literature review to identify other potential sources of disutilities associated with providing care for people with MS.

13.1.14 Treatment effect

The effect of treatment with disease modifying treatments was modelled for the relative reduction in the annual frequency in relapses and the relative risk of disease progression between EDSS states. In the RSS model, both treatment effects were estimated based on observed relapses and progressions in EDSS scores in people in the Risk Sharing Scheme. Though not clear, it appeared that similar methods used to derive transition matrices from the BCMS cohort were used to derive transition matrices for the RSS model. From the comparison between both cohorts, a mean hazard ratio of 0.7913 for disability progression was derived, based on the RSS Y10 analyses. The model assumed that the treatment effect reduced the instantaneous rate of forward transitions by this hazard ratio, independent of EDSS, and that there was no effect on backward transitions. The report suggested that the hazard ratios for backward transitions wase similar to that as for forward transitions, however, these ratios were not reported. Additionally, in the model (base run) it was assumed that the hazard ratio remained the same over the entire duration (50 years) of the model time horizon.

13.1.15 Relapse frequency

In the RSS model, a weighted average of the frequency of relapse for people with RRMS and SPMS, irrespective of EDDS level was derived based on information obatained from the 2002 survey by the MS Trust

(see Table 30). However, due to the paucity of information reported on the aggregate treatment effect of DMTs in reducing relapse frequencies, we are unable to provide further commentary on this estimate.

Table 30: Relapse frequency by EDSS state

EDSS	Relapse frequency		Relapse frequency (%)		Untreated	Treated
	RRMS	SPMS	% RRMS	% SPMS	Mean frequency	Mean frequency
0	0.8895	0.0000	1.000	0.000	0.8895	0.6405
1	0.7885	0.0000	0.861	0.139	0.6790	0.4888
2	0.6478	0.6049	0.861	0.139	0.6418	0.4621
3	0.6155	0.5154	0.806	0.194	0.5961	0.4292
4	0.5532	0.4867	0.545	0.455	0.5230	0.3765
5	0.5249	0.4226	0.343	0.657	0.4577	0.3295
6	0.5146	0.3595	0.270	0.730	0.4014	0.2890
7	0.4482	0.3025	0.053	0.947	0.3103	0.2234
8	0.3665	0.2510	0.000	1.000	0.2510	0.1807
9	0.2964	0.2172	0.000	1.000	0.2172	0.1564
10	0.0000	0.0000	0.000	0.000	0	0

13.1.16 Treatment discontinuation

In the treatment arm of the economic model it was assumed that 5% of people discontinue treatment every year as a result of adverse events, and that treatment would be discontinued amongst individuals progressing to EDSS ≥7. However, the reasons for this were unclear; for example people may discontinue treatment because the therapy is no longer working.[257]

The assessment group noted that no sensitivity analyses or probabilistic sensitivity analysis was undertaken around these key assumptions about discontinuation. The justification for this assumption was based on the proportion of people discontinuing treatment as seen in the RSS. However, published evidence suggests thatthe proportion of people discontinuing treatment in clinical trials of the DMTs included in the RSS may range from 0% (Singer et al., 2012).[195] to 10% (Fox et al., 2012).[214] Additionally, it appears that people who discontinued treatment continued to accrue treatment benefits without additional costs. When people progressed to EDSS 7-9, the model used 'on treatment' transition probabilities. The assessment group would expect that people who discontinued treatment would progress to more severe health states in a similar way to people in the natural history cohort.

13.1.17 Analysis (cycle length, time horizon and perspective)

For the base case analysis, a Markov model was developed and programmed to assess the cost-effectiveness of the combined treatment effect of DMTs in the RSS compared to no treatment for people with RRMS. The model cycled yearly, with a starting age of 30-years and estimated the mean costs and effects associated with treatment compared with no treatment (best supportive care) over a 50-year time horizon. The analysis was conducted from the NHS and Personal Social Services (PSS) perspective and the results reported in terms of an incremental cost-effectiveness ratio, expressed as costs per QALYs gained. Both costs and benefits were discounted at 3.5% per annum.

13.1.18 Time varying model

The RSS submission also included a sensirtivity analysis using a 'time varying model' to take account of a perceived lack of fit of the RSS in taking account of trajectories of patients with higher EDSS at baseline. The model had two sets of transition probabilities, one for years 0-2 and one for all subsequent years.

13.2 *Summary of the critical appraisal of the RSS model*

In general, the assessment group considered the model submitted by the RSS to be appropriate in order to estimate the cost-effectiveness of DMTs compared to best supportive care. In most cases, the model draws on the best available evidence on progression through RRMS and SPMS by EDSS levels, resource use and costs, and utility values. We haveconsidered and provided a critique of the RSS model against the NICE reference case, and of the economic model inputs and we checked the model used to estimate the cost-effectiveness. However, e some uncertainties remain, which are presented below. Additionally in Chapter 15, we describe alternative analyses, which address our concerns. Our concerns are summarised below:

1. The model applied a constant rate of 5% for people discontinuing treatment. However, there is little evidence to support this assumption.
2. The difference between combined DMTs and best supportive care in reducing the frequency of relapses was 0.72, but it was unclear how this value was derived. The report suggested that a weighted average of the frequency of relapses for people with RRMS and SPMS, irrespective of EDDS level, was used and that this was derived from information obtained from the 2002 survey undertaken by the MS Trust.
3. The assessment group noted that there was an increased risk of mortality for people with MS when compared to the general population, as well as transition probabilities to EDSS 10 (MS-related death). Using this assumption would lead to double-counting MS-related deaths in the model.
4. The model considers the agreed price between the companies and the Department of Health. However, it was unclear to the assessment group how these prices were derived.
5. In the analysis, the model included carers' distutilities. The assessment group agrees that people may experience a loss in utility for caring of people with multiple sclerosis. However, in this instance, the perspective of the analysis is from the NHS and PSS perspective.
6. A probabilistic sensitivity analysis, to incorporate uncertainty in the estimates for model parameters, was not undertaken.

14 COMPANY SUBMISSIONS

14.1 Biogen Idec Ltd

14.1.1 Background

This section focuses on the economic evidence submitted by Biogen Idec Ltd. This section is set out as follows: first, we present an overview/summary then a critique of the economic model submitted which describes in detail the evidence (e.g. natural history information, effectiveness of interventions included in the analysis, resource use and costs, mortality and health-related quality of life) used to parameterise the models. In the Biogen Idec Ltd. model, an economic analysis was conducted to assess the cost-effectiveness of disease modifying treatments—IFN β-1a 30 µg IM once weekly (Avonex), IFN β-1a 44 or 22 µg SC three times weekly (Rebif), IFN β-1b 250 µg SC every other day (Betaferon/Extavia), pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy) and GA 20 mg SC daily or 40 mg SC three times weekly (Copaxone)—compared with best supportive care for people with RRMS.

In the analysis, a Markov model was used to depict the natural history of people with RRMS through the progression to secondary multiple sclerosis. Information required on the natural history of people with RRMS was based on extrapolating the ADVANCE placebo arm data with the British Columbia cohort.

In the intervention arms, it was assumed that treatment with DMTs was not discontinued due to reaching a particular EDSS level, which the authors suggested is in accordance with the current Association of British Neurologists (ABN) guidelines.[262] It was assumed that people would only discontinue treatment having progressed to the secondary progressive multiple sclerosis health state.

The analysis was undertaken from the payer perspective. The outcome measure used in the analysis was quality-adjusted life-years (QALYs) gained, over a 50-year time horizon. Treatment effects were assumed to delay the progression of the disease and reduce the frequency of relapses. Information on utilities for RRMS by EDSS level were based on information from the ADVANCE trial[211] and Orme et al. (2007),[105], which were derived from utility values from the UK MS survey. Utility values for SPMS by EDSS level were based on information from the UK MS survey as cited in the company submission. Carers' disutilities were based on information obtained from the manufacturer's submission to NICE for TA127.[263] Utility values for adverse events associated with each DMD were included in the economic analysis.

Information on resource use and unit costs were obtained from various sources. The results were presented as an ICER and expressed as cost per life years gained (LYG) and cost per QALYs gained. Both costs and benefits were discounted at 3.5% per annum. Authors have undertaken a number of sensitivity analyses (societal perspective, patient baseline characteristics, transition probabilities, treatment efficacy, relapse rates, discontinuation rates, utility values, mortality multipliers, patients' out-of-pocket costs, carers' costs, loss of productivity for people with MS and adverse events) and probabilistic sensitivity analysis to determine the robustness of the base-case results.

Base-case results showed that treatment with pegylated IFN β-1a SC 125µg every two weeks resulted in the highest mean life-years gained (20.658) and mean QALYs (9.642) compared to all other interventions included

in the analysis. Pegylated IFN β-1a SC 125 µg every two weeks compared to best supportive care had a mean incremental cost of approximately £25,200 with corresponding incremental 0.810 QALYs, which equated to an ICER of approximately £31,000 per QALY.

Results from the sensitivity analyses showed that the base-case results were robust to univariate changes made to key input parameters except the hazard ratio for the confirmed disability progression, which had the greatest impact. The probabilistic sensitivity analysis suggested that at a £30,000/QALY willingness to pay threshold, pegylated IFN β-1a 125 µg SC every two weeks had a <0.4 probability of being cost-effective when compared to best supportive care.

14.1.2 Types of multiple sclerosis

The model includes people who commenced in a relapsing-remitting multiple sclerosis health state and progressed to secondary progressive multiple sclerosis. People with clinically isolated syndrome, primary progressive multiple sclerosis or benign disease were not included in the analysis.

14.1.3 Model structure

The illustrative Markov model structure submitted by the company was based on the original ScHARR model,[257] with developments to include other interventions. The company used a cohort-based Markov model to depict the natural history of people with RRMS. The model simulated the disability progression, progression from RRMS to SPMS, and the relapsing nature of the disease. People with RRMS were able to occupy one of the EDSS health states, which ranged from 0 to 10, and in increments of 0.5. The model allowed for people to progress, regress or stay in the same EDSS health state, or progress from EDSS to SPMS. When people progress to SPMS, they either remained or progressed to more severe SPMS EDSS states.

In the model, people incurred costs and accrued benefits depending on the EDSS state for RRMS and SPMS. Benefits were measured using quality-adjusted life years, whereby each model cycle a utility is assigned to people occupying a specific health state.

The assessment group was uncertain if the review of the economic literature was undertaken to inform the model design and/or its inputs. Based on our review there appears to be some inconsistency in the model structures that have been used to estimate the cost-effectiveness of DMTs for people with RRMS. These discrepancies may be a result of the complex nature of multiple sclerosis. In Biogen Idec's model, people could progress from health states EDSS ≥1 to SPMS. However, in some models identified in the review people could only progress from EDSS ≥6 to SPMS.

14.1.4 Interventions

The interventions considered in the economic analyses included IFN β-1a 30 µg IM once weekly (Avonex), IFN β-1a 44 or 22 µg SC three times weekly (Rebif), IFN β-1b 250 µg SC every other day (Betaferon/Extavia), pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy) and GA 20 mg SC daily or 40 mg SC three times weekly (Copaxone). These comparisons are all in line with the NICE scope. The interventions are compared

against best supportive care for people with RRMS. The company suggested that best supportive care would not currently be offered as a start point to RRMS patients.

14.1.5 Population

The population included in the economic analysis was similar to the population included in the ADVANCE trial (i.e. 71% of females with a starting age of 36 years with relapsing-remitting multiple sclerosis). The initial distribution of people in each EDSS state is presented in Table 31.

Table 31: Baseline distribution of people by EDSS state, Biogen model

EDSS	Distribution (%)
0	6%
1	26%
1.5-2	28%
2.5-3	24%
3.5-4	12%
4.5-5	4%
5.5-6	0%
6.5-7	0%
7.5-8	0%
8.5-9.5	0%
10	0%

14.1.6 Transitions

To simulate how people transitioned between the health states in the model, information was required on transitions between RRMS health states, progressing from RRMS to SPMS and transitions between SPMS, for both the comparator and intervention arms (discussed in the treatment efficacy section). In the comparator arm (natural history receiving best supportive care), in the base case, transitions were derived from information from the ADVANCE trial,[211] and supplemented with information from the British Columbia dataset.[151] Table 32 shows the annual transition probabilities between RRMS health states used in the natural history arm. In sensitivity analysis, the company has derived other transit probabilities, using information from the ADVANCE trial extrapolated with the British Columbia dataset or London Ontario dataset.[84] For the transition probabilities from RRMS to SPMS these were based on information from the London Ontario dataset. The company suggested that these values were not available in the British Columbia MS cohort and, they have not elaborated on how these transition probabilities were derived. Table 33 shows the transitions between RRMS to SPMS by EDSS level. Transition probabilities for people progressing within SPMS health states were estimated from the British Columbia cohort. These annual probabilities were derived using a multistate model. Table 34 shows the transitions between SPMS states.

Table 32: Natural history matrix based on information from ADVANCE trial and British Columbia dataset, Biogen model

EDSS From/to		EDSS state (to)										
		0	**1**	**1.5-2**	**2.5-3**	**3.5-4**	**4.5-5**	**5.5-6**	**6.5-7**	**7.5-8**	**8.5-9.5**	**10**
EDSS state (from)	**0**	0.850	0.050	0.100	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0
	1	0.024	0.830	0.114	0.024	0.000	0.000	0.006	0.001	0.001	0.000	0
	1.5-2	0.014	0.152	0.670	0.104	0.048	0.000	0.010	0.001	0.001	0.000	0
	2.5-3	0.000	0.008	0.125	0.693	0.084	0.017	0.064	0.005	0.004	0.000	0
	3.5-4	0.000	0.022	0.000	0.216	0.519	0.086	0.141	0.009	0.007	0.000	0
	4.5-5	0.000	0.000	0.000	0.000	0.041	0.532	0.375	0.028	0.023	0.000	0
	5.5-6	0.000	0.000	0.000	0.000	0.000	0.000	0.894	0.049	0.056	0.001	0
	6.5-7	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.807	0.189	0.004	0
	7.5-8	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.995	0.006	0
	8.5-9.5	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000	0
	10	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1

Table 33: Annual transition probabilities for RRMS to SPMS, Biogen model

EDSS	Probability of transition to SPMS (one EDSS higher)
1	0.003
1.5-2	0.032
2.5-3	0.117
3.5-4	0.210
4.5-5	0.299
5.5-6	0.237
6.5-7	0.254
7.5-8	0.153
8.5-9.5	1.000

Table 34: Annual transition probabilities between SPMS health states based on information from the British Columbia dataset, Biogen model

EDSS From/to		EDSS state (to)										
		0	**1**	**1.5-2**	**2.5-3**	**3.5-4**	**4.5-5**	**5.5-6**	**6.5-7**	**7.5-8**	**8.5-9.5**	**10**
EDSS state (from)	**0**	0.695	0.203	0.073	0.022	0.004	0.001	0.002	0.000	0.000	0.000	0
	1	0.058	0.695	0.158	0.061	0.016	0.005	0.006	0.000	0.000	0.000	0
	1.5-2	0.016	0.121	0.608	0.168	0.045	0.018	0.022	0.002	0.001	0.000	0
	2.5-3	0.006	0.050	0.120	0.544	0.091	0.058	0.116	0.010	0.004	0.000	0
	3.5-4	0.002	0.022	0.067	0.115	0.489	0.104	0.168	0.026	0.007	0.001	0
	4.5-5	0.001	0.005	0.029	0.059	0.087	0.487	0.273	0.039	0.019	0.001	0
	5.5-6	0.000	0.001	0.004	0.025	0.031	0.041	0.741	0.109	0.044	0.004	0
	6.5-7	0.000	0.000	0.001	0.002	0.007	0.004	0.117	0.693	0.161	0.016	0
	7.5-8	0.000	0.000	0.000	0.000	0.001	0.001	0.019	0.056	0.903	0.021	0
	8.5-9.5	0.000	0.000	0.000	0.000	0.000	0.000	0.002	0.006	0.174	0.818	0
	10	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1

14.1.7 Treatment effects of IM IFN β -1a 30µg

For disability progression the company derived a hazard ratio based on a Cox proportional hazard model as a measure of relative risk. In the RSS model, the treatment effect of IFN β-1a 30µg IM once weekly (Avonex) was shown to be [redacted].
The year 10 implied hazard ratio of [redacted] for IFN β-1a 30µg IM once weekly (Avonex) was used in the company's model. Assuming no waning, the transition matrices are presented in Table 35 and Table 36, for age of onset <28 and >28 years, respectively. The implied hazard ratio was applied to the model to show the relative effect of treatment on disability progression.

Table 35: Transition matrix for IFN β-1a 30 µg IM once weekly, age at onset <28 years, Biogen model

EDSS		EDSS state (from)										
		0	1	1.5-2	2.5-3	3.5-4	4.5-5	5.5-6	6.5-7	7.5-8	8.5-9.5	10
EDSS state (to)	0											
	1											
	1.5-2											
	2.5-3											
	3.5-4											
	4.5-5											
	5.5-6											
	6.5-7											
	7.5-8											
	8.5-9.5											
	10											

Table 36: Transition matrix for IFN β-1a 30 µg IM once weekly, age at onset >28 years, Biogen model

EDSS		EDSS state (from)										
		0	1	1.5-2	2.5-3	3.5-4	4.5-5	5.5-6	6.5-7	7.5-8	8.5-9.5	10
EDSS state (to)	0											
	1											
	1.5-2											
	2.5-3											
	3.5-4											
	4.5-5											
	5.5-6											
	6.5-7											
	7.5-8											
	8.5-9.5											
	10											

14.1.8 Resource use and costs

All costs included in the analysis were those directly related to the NHS and PSS perspective, and were reported in pounds sterling in 2015/16 prices. The model included the following resource use and costs in order to conduct their analyses:

- Drug acquisition costs
- Administration costs
- Monitoring costs
- Health state/EDSS costs
- Cost of relapse
- Treatment-related adverse event costs

14.1.9 Drug acquisition costs

Treatment costs for IFN β-1a 30 µg IM once weekly (Avonex) and pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy) along with the other DMTs are presented in Table 37. Annual costs were presented for the list and net price for each DMT available at the time of the RSS. From the Excel model submitted, costs of treatments were based on the dosage (per week and year), price per packet, and the annual costs for each drug was derived. The assessment group considered these acquisition costs to be correctly derived.

Table 37: Annual treatment costs in the Biogen model

Treatment	Administration	Doses per year	Annual acquisition costs (list price: £, 2014/15 prices)		Annual acquisition costs (net price: £, 2014/15 prices)	
			Year 1	Subsequent years	Year 1	Subsequent years
IM IFN β-1a (Avonex)	30 µg once weekly	52.18	8502	8502	[redacted]	[redacted]
SC IFN β-1a (Plegridy)	125 µg every two weeks	26.1	8502	8502	8502	8502
SC IFN β-1a (Rebif)	22 µg three times weekly	156.18	7914	7976	7513	7513
SC IFN β-1a (Rebif)	44 µg three times weekly	156.18	10,311	10,572	8942	8942
SC IFN β-1b (Betaferon)	250 µg every other day	182.63	7239	7239	7259	7259
SC IFN β-1b (Extavia)	250 µg every other day	182.63	7239.11	7239.11	7239.11	7239.11
GA (Copaxone)	20 mg once daily	365.25	6681	6681	5823	5823
GA (Copaxone)	40 mg once daily	156.18	6681	6681	6681	6681
GA, glatiramer acetate; IM, intramuscular; SC, subcutaneous						

Where no net prices for DMTs were available the list price of these drugs were used in the analysis. The ERG noted that the annual drug acquisition costs for IFN β-1b 250 µg SC every other day (Betaferon) are reported in Table 37 as £7239 but the model used £7239.11 in the analysis.

14.1.10 Administration costs

Annual administration costs included costs associated with training/teaching people self-administration. The administration costs are presented in Table 38. The assessment group considered the resource use and costs to be appropriate.

Table 38: Administration costs for each intervention, Biogen model

Treatment	Annual administration cost for Year one (£, 2014/15)	Resource use	Annual administration cost for subsequent years (£, 2014/15)	Resource use
IFN β-1a 30 µg IM once weekly (Avonex)	177.00	3 hours of nurse's time to teach self-administration	0.00	None
IFN β-1a 44 or 22 µg SC three times weekly (Rebif)				
IFN β-1b 250 µg SC every other day (Betaferon/Extavia)				
Pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy)				
GA 20 mg SC daily or 40 mg SC three times weekly (Copaxone)				

14.1.11 Monitoring costs

Annual monitoring costs for each treatment were presented in Appendix K of the main report. The company clearly outlined the resource use, used to derive monitoring costs. Monitoring costs were presented for Year one and for subsequent years. The monitoring costs for all interventions are presented in Table 39. These annual monitoring costs appeared to have been derived and used in the model correctly.

Table 39: Annual costs for monitoring each treatment, Biogen model

Drug intervention	Monitoring costs for Year 1 (£, 2014/15)	Monitoring costs for subsequent years (£, 2014/15)
IFN β-1a 30 µg IM once weekly (Avonex)	190.73	10.78
IFN β-1a 44 or 22 µg SC three times weekly (Rebif)	203.25	10.78
IFN β-1b 250 µg SC every other day (Betaferon/Extavia)	190.73	10.78
Pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy)	191.92	10.78
GA 20 mg SC daily or 40 mg SC three times weekly (Copaxone)	175.75	10.78

14.1.12 Health state/EDSS costs

Health state costs (payers' perspective) by EDSS level and type (RRMS/SPMS) are presented in Table 40. These costs were related to MS management (expected/unexpected visits to healthcare providers). The company also identified and presented cost estimates from other sources (Karampampa et al., 2012)[264] and the burden of illness (BOI) study). Costs obtained from Karampampa et al. were inflated using the hospital and community health services (HCHS) index, and these seemed to be correctly derived. These costs estimated were used in sensitivity analyses. Costs were presented from the payer, government and societal perspectives. It appears, that these cost estimates by EDSS states vary between studies. For the cost estimates derived in the submission and the BOI study, there appears to be a gradual increase in management costs for EDSS 0 to 6, then increases beyond EDSS 6. However, in the Karampampa study, management costs seemed to increase gradually from EDSS 0 to 10.

Table 40: Mean unit costs in the model from payers' perspective, Biogen model

EDSS state	RRMS (£, 2014/15)			SPMS (£, 2014/15)		
	Biogen	Karampampa et al., 2012	BOI study	Biogen	Karampampa et al., 2012	BOI study
0	937	1179	4301	1263	1470	4301
1	974	1399	4783	1301	1745	4783
1.5-2	714	1674	8666	1040	2088	8666
2.5-3	3906	2006	7720	4232	2502	7720
3.5-4	1892	2393	7159	2218	2985	7159
4.5-5	3210	2837	9147	3537	3538	9147
5.5-6	4285	3337	12,830	4611	4161	12,830
6.5-7	11,279	3892	17,971	11,605	4854	17,971
7.5-8	27,472	4503	29,915	27,798	5616	29,915
8.5-9.5	21,982	5170	37,656	22,309	6449	37,656
10	0	0	0	0	0	0

14.1.13 Cost of relapse

In the main report of the company's submission, the costs of a relapse was obtained from the ScHARR model[257] (£2697) and subsequently inflated to current prices (£4265) using the Hospital and Community Health Services pay and price index 2014/15.[260] Using costs from a dated source, suggests that the management and resource use for treating relapses have not change post-2009. The assessment group considered this to be a strong assumption..

In critiquing the economic model submitted (and stated in the appendices), the assessment group noted that the cost of relapse used were obtained from the Hawton and Green (2015) study,[111] then subsequently inflated to current prices using the Hospital and Community Health Services (HCHS) pay and price index 2014/15.[260] The cost represents an average cost regardless of the severity of the relapse. Costs were derived for relapses not requiring (£568) and those requiring hospitalisation (£3651). The assessment group noted that these costs were the same in all arms (interventions and comparator) of the model. These costs appear to have been correctly derived. However, the company did not elaborate on the resource use estimates used to derive the unit cost of a

relapse. Resource use information in the Hawton and Green study was obtained from information collected in the UK South West Impact of Multiple Sclerosis (SWIMS) project.[265] SWIMS is a prospective, longitudinal cohort study of people with MS in Devon and Cornwall, with people followed-up every six months. In this study information was collected on the type of MS, disease severity measured by the EDSS, number of relapses in the previous six months, length of relapse, whether relapses led to hospital admittance, and the treatment received for relapses. Additional information was collected on health or social care use in the previous six months and the frequency of contact with a health care professional. Resource use was valued using the Personal Social Services Unit, NHS Reference costs and the British National Formulary.[24] All costs derived were reported in UK pound sterling using 2012 prices. The ERG considers this study to be methodologically robust. However, these costs represented people with various types of MS (RRMS, PPMS, SPMS, Benign or combination or not known) who experienced relapses over a six month period. Resource use and costs were not reported by type of MS in the Hawton and Green study.[111] The assessment group considers these costs used in the model to be an underestimate of the cost of a relapse.

14.1.14 Adverse events and cost of adverse events

The model included costs for adverse events as a result of disease modifying treatment. In Appendix K of the company's submission, estimates on resource use were presented. Healthcare resource use for each adverse event was validated by a Delphi panel conducted by the company in December 2013. The company provided the percentages of people who developed these adverse events by DMTs. Table 41 shows the annual costs of treatment for adverse events used in the model by DMT. These annual costs for treatment of adverse events appear to be correctly derived.

Table 41: Annual cost of treatment for adverse events by DMT, Biogen model

DMT	Unit cost (£, 2014/15)
IM IFN β-1a 30 μg once weekly (Avonex)	154.97
SC pegylated IFN β-1a 125 μg every two weeks (Plegridy)	76.95
SC IFN β-1a 22 μg three times weekly (Rebif)	127.33
SC IFN β-1a 44 μg three times weekly (Rebif)	140.89
SC IFN β-1b 250 μg every other day (Betaferon)	104.12
SC IFN β-1b 250 μg every other day (Extavia)	104.12
GA 20 mg SC once daily (Copaxone)	74.78
GA 40 mg SC once daily (Copaxone)	74.78

14.1.15 Health state utility values

Utilities were derived by EDSS level and MS type (RRMS and SPMS). In the base case, these were derived by combining information from the placebo arm of the ADVANCE trial[211] (EDSS 0-5) with information from the UK MS survey (EDSS ≥6). Utility values for EDSS 6 were derived by adding the utility value from EDSS 5 (taken from ADVANCE study) to the difference between EDSS 6 and 5 from the UK MS Survey. The same method was used to derive utility values for EDSS scores ≥7 to 9). Utility values used in the model are presented in Table 42. The company also included disutilities associated with relapses experienced in an RRMS health state (-0.071) and those in a SPMS health state (-0.045). These disutilities were applied across all EDSS levels by MS type (RRMS and SPMS). Disutilities were obtained from the Orme study.[105] An analysis was

undertaken which included carers' disutilities by EDSS state. Table 42 shows the disutility values used in the model. Due to the lack of information, carers' burdens associated with caring for people with either RRMS and SPMS were assumed to be the same.

Table 42: Mean utility values used, Biogen model

EDSS state	Utility value		Carer's disutility	
	RRMS	SPMS	RRMS	SPMS
0	0.879	0.834	0.000	0.000
1	0.866	0.821	-0.001	-0.001
1.5-2	0.771	0.726	-0.003	-0.003
2.5-3	0.662	0.617	-0.009	-0.009
3.5-4	0.573	0.528	-0.009	-0.009
4.5-5	0.549	0.504	-0.020	-0.020
5.5-6	0.491	0.446	-0.027	-0.027
6.5-7	0.328	0.283	-0.053	-0.053
7.5-8	-0.018	-0.063	-0.107	-0.107
8.5-9.5	-0.164	-0.209	-0.140	-0.140
Relapse disutility in the RRMS states				-0.071
Relapse disutility in the SPMS states				-0.045

14.1.16 Adverse event disutility

The disutilities associated with adverse events by DMTs are presented in Table 43.

Table 43: Annual disutility values associated with each DMT, Biogen model

Disease modifying treatments	Annual disutility
IFN β-1a 30 µg IM once weekly (Avonex)	-0.024
Pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy)	-0.016
IFN β-1a 44 µg SC three times weekly (Rebif)	-0.019
IFN β-1b 250 µg SC every other day (Betaferon)	-0.018
IFN β-1b 250 µg SC every other day (Extavia)	-0.018
GA 20 mg SC once daily (Copaxone)	-0.007
GA 40 mg SC once daily (Copaxone)	-0.007

14.1.17 Mortality rate

Mortality was assumed to be equivalent between RRMS and SPMS and dependent on EDSS state. All patients were modelled to be at risk of mortlity from MS and other causes. This was modelled by first estimating standardised mortlity rates using data from the Office of National Statistics, as cited in the Biogen submission, and applying a mortality multiplier to reflect both causes of death. Additional, individuals in EDSS states 7-9, could die from MS-specfic mortlity from transition to EDSS state 10 (death).

14.1.18 Relapse frequency

The annualised relapse rates (ARR) were obtained from the ADVANCE trial[211] up to EDSS 5.5, and supplemented with rates derived from the Patzold et al. (2008), as cited in the manufacturer submission, and the

ADVANCE trial. Table 44 shows the relapse rates by EDSS level used in the base case and other relapse rates used in scenario analyses.

Table 44: Relapse frequency by EDSS state and type of MS (RRMS and SPMS) for BSC, Biogen model

EDSS	ADVACE placebo		Patzold 1982 and UK MS survey (TA254, TA320 methods)		Patzold 1982 and UK MS survey (TA303, TA312 methods)	
	RRMS	SPMS	RRMS	SPMS	RRMS	SPMS
0	0.260	0.000	0.709	0.000	0.725	0.000
1	0.237	0.000	0.729	0.000	0.743	0.000
1.5-2	0.460	0.315	0.676	0.465	0.690	0.447
2.5-3	0.495	0.602	0.720	0.875	0.723	0.788
3.5-4	0.670	0.515	0.705	0.545	0.707	0.567
4.5-5	0.181	0.160	0.591	0.524	0.599	0.517
5.5-6	0.150	0.139	0.490	0.453	0.508	0.445
6.5-7	0.156	0.104	0.508	0.340	0.504	0.312
7.5-8	0.156	0.104	0.508	0.340	0.504	0.312
8.5-9.5	0.156	0.104	0.508	0.340	0.504	0.312
10	0	0	0	0	0	0

Relapse rates per person per year for EDSS levels >5.5 were derived based on the relative increase in ARR reported in the Patzold study (Patzold et al., 1982).[266] Patzold reported ARR based on the year of diagnosis of RRMS. ARR by year were converted to ARR by EDSS level by taking the mean number of relapses per year for each health state from the UK MS survey and multiplying by the relative relapse rates per person reported by Patzold.

14.1.19 Treatment discontinuation

In the model, people who progressed to a SPMS health state discontinued treatment. However, treatment was assumed not to discontinue due to reaching a particular EDSS level. This is in accordance to current ABN guidelines.[262] Annual discontinuation rates used in the model are presented in Table 45.

Table 45: Annual discontinuation by DMT, Biogen model

Disease modifying treatments	Annual withdrawal (%)
IM IFN β-1a 30µg once weekly (Avonex)	7.9
Pegylated IFN β-1a SC 125 µg every two weeks (Plegridy)	10.4
IFN β-1a 22 µg SC three times weekly (Rebif)	6.0
IFN β-1a 44 µg SC three times weekly (Rebif)	12.3
IFN β-1b 250 µg SC every other day (Betaferon)	5.7
IFN β-1b 250 µg SC every other day (Extavia)	5.7
GA 20 mg once daily (Copaxone)	7.2
GA 40 mg once daily (Copaxone)	7.2
GA, glatiramer acetate; IM, intramuscular; SC, subcutaneous	

14.1.20 Analysis (cycle length, time horizon and perspective)

The analysis was undertaken from the National Health Service (NHS) and Personal Social Services (PSS) perspective. The outcome measure used in the analysis was quality-adjusted life-years gained, over a 50-year time horizon with annual cycle lengths. The starting age of the population was 36 years. Results were presented

as an incremental cost-effectiveness ratio (ICER) and expressed as cost per quality-adjusted life-years (QALYs) gained. Both costs and benefits were discounted at 3.5% per annum.

14.1.21 Assumptions

In order to have a workable model, the company made the following assumptions:

1. The probability of transitioning to a health state in the next cycle depends only on the health state of the present cycle
2. Transition from RRMS to SPMS is accompanied by an increase in EDSS scale of 1.0
3. The population at baseline in ADVANCE is representative of the RRMS population in clinical practice
4. Each year, EDSS score can remain the same, increase or decrease
5. In the base case, treatments affect EDSS progression but not EDSS regression
6. Treatment effects on relapse and EDSS progression are independent
7. In the base case, treatments have the same effect on progression in each EDSS state
8. In the base case, treatment efficacy is constant over time
9. Treatments do not directly impact transitions to SPMS, but impact patients' EDSS state, which influences transition to SPMS
10. Treatment discontinuation is constant for all years
11. It is assumed that mortality rates for age>100 is same as age=100
12. The annualised adverse event risks are applied every year - this may overestimate the incidence of adverse events since patients who have adverse events may discontinue in the initial years on treatment
13. RRMS patients in all EDSS states may receive treatments depending upon the maximum EDSS limit selected on sheet 'Settings'
14. SPMS patients receive BSC only
15. Patient access schemes, where publicly available, are considered in the base case

14.1.22 Summary of Biogen submission results

Base-case results showed that treatment with pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy) resulted in the highest mean life-years gained (20.658) and mean QALYs (9.642) compared to all other interventions included in the analysis. Pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy) compared to best supportive care had a mean incremental cost of approximately £25,200 with corresponding incremental 0.810 QALYs, which equated to an ICER of approximately £31,000 per QALY.

Results from the sensitivity analyses showed that the base-case results were robust to univariate changes made to key input parameters except the hazard ratio for the confirmed disability progression, which had the greatest impact. The probabilistic sensitivity analysis suggested that at a willingness to pay threshold of £30,000/QALY, pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy) had a <0.4 probability of being cost-effective when compared to best supportive care.

14.2 Teva UK Limited

14.2.1 Background

This section focuses on the economic evidence submitted by Teva UK Ltd. on glatiramer acetate (Copaxone). This section is set out as for the previous copmpnay submission follows: first, we present an overview/summary then a critique of the economic model submitted by Teva UK Ltd. This section describes in detail the evidence (e.g. natural history information, effectiveness of interventions included in the analysis, resource use and costs, mortality and health-related quality of life) used to parameterise the models.

The economic submission to NICE included:

- A description of an economic model from Teva UK Ltd. which assesses the cost-effectiveness of disease modifying drugs for the treatment of RRMS; this includes details on the intervention and comparators, study population, resource use and costs, the modelling methodology, and assumptions.
- Appendices with details of the evidence used to inform the model, and a description of a network meta-analysis carried out to generate alternative estimates of efficacy which are used in sensitivity analysis.

14.2.2 Overview

In the Teva UK Ltd. model, an economic analysis was conducted to assess the cost-effectiveness of disease modifying treatments—IFN β-1a 30 µg IM once weekly (Avonex), IFN β-1a 44 or 22 µg SC three times weekly (Rebif), IFN β-1b 250 µg SC every other day (Betaferon/Extavia), pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy) and GA 20 mg SC daily or 40 mg SC three times weekly (Copaxone), as well as fingolimod, nataliumab and dimethyl fumarate—compared with best supportive care for people with RRMS.

In the analysis, a Markov model was used to depict the natural history of people with RRMS through progression to secondary progressive multiple sclerosis (SPMS). The model includes 21 health states, defined by EDSS score and disease stage (RRMS or SPMS). Only integer EDSS values were allowed, and fractional values were rounded down. Disease progression rates during RRMS on best supportive care were based on the British Columbia multiple sclerosis database, as in the RSS.[151] Transition rates to SPMS were estimated using hazard rates observed in the London Ontario dataset,[84] following assumptions made in the ScHARR model.[257] The Teva UK model assumes that progression to SPMS increases EDSS scores by 1. Progression between EDSS scores for SPMSS were calculated using the same transition probabilities as for RRMS. Treatment was assumed to continue until patients progressed to SPMS, or reached an EDSS score of 7 or greater, and was not reinitiated.

The analysis was undertaken from the payer perspective, although sensitivity analyses were included from a societal perspective. The outcome measure used in the analysis was QALYs gained, over a 50-year time horizon. Treatment effects were assumed to delay the progression of the disease and reduce the frequency of relapses. The assumed hazard ratio (applied to all forward transitions) of glatiramer acetate (Copaxone) vs. best supportive care was [redacted] in the base case, based on the subset of patients in the RSS who received this DMT. Utilities for RRMS by EDSS level were based on pooling data from the MS Trust and Orme et al.,[105] following the RSS. Utility values for SPMS by EDSS level were assumed to be the same as for RRMS. Carers' disutilities

were based on information obtained from the manufacturer's submission to NICE for TA127.[263] Utility values for adverse events associated with each DMT were taken from a range of sources, including the NICE appraisal of alemtuzumab, and Maruszczak et al.[267]

Information on resource use and unit costs were obtained from various sources (British National Formulary,[24] PSSRU, NHS reference costs). The results were presented as an ICER and expressed as cost per life years gained (LYG) and cost per QALYs gained. Both costs and benefits were discounted at 3.5% per annum. Authors undertook a number of sensitivity analyses (societal perspective, patient baseline characteristics, transition probabilities, treatment efficacy, relapse rates, discontinuation rates, utility values, mortality multipliers, patients' out-of-pocket costs, carers' costs, loss of productivity for people with MS and adverse events) and probabilistic sensitivity analysis to determine the robustness of the base-case results. Base-case results showed that treatment with glatiramer acetate (Copaxone) resulted in a mean gain per patient of [redacted] life years or [redacted] QALY, at a net discounted cost of [redacted], giving an ICER [redacted] per QALY. The probability of cost-effectiveness for glatiramer acetate (Ccopaxone) relative to best supportive care was [redacted] at £20,000 per QALY and [redacted] at £30,000 per QALY. Results from deterministic sensitivity analyses showed that the base-case results were robust to univariate changes made to key input parameters except the hazard ratio for the confirmed disability progression, which had the greatest impact, and EDSS score related costs, which did influence whether glatiramer acetate (Copaxone) was cost-effective relative to best supportive care (see below).

14.2.3 Evidence used to parameterise the Risk Sharing Scheme (RSS) multiple sclerosis model

Natural history of relapsing-remitting multiple sclerosis

Two key sources informed the analysis of natural history of RRMS; the London Ontario dataset[84] for transition to SPMS, and the British Columbia[151] dataset for EDSS progression. Table 46 and Table 47 show the natural history transition matrices from the British Columbia dataset.

Table 46: Natural history transition matrix based on information from the British Columbia dataset (below median age)

EDSS from/to		EDSS state (to)										
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
EDSS state (from)	**0**	0.68701	0.21104	0.07196	0.02236	0.00434	0.00136	0.00176	0.00012	0.00003	0.00000	0.00000
	1	0.06122	0.67867	0.16643	0.06463	0.01698	0.00474	0.00667	0.00052	0.00014	0.00001	0.00000
	2	0.01692	0.12654	0.59552	0.17292	0.04538	0.01842	0.02190	0.00182	0.00054	0.00005	0.00000
	3	0.00620	0.05215	0.11649	0.54385	0.09451	0.05729	0.11479	0.01070	0.00366	0.00035	0.00000
	4	0.00176	0.02251	0.06617	0.12104	0.48739	0.10090	0.16645	0.02622	0.00689	0.00067	0.00000
	5	0.00055	0.00562	0.02915	0.05935	0.09154	0.47268	0.28098	0.03961	0.01909	0.00143	0.00000
	6	0.00012	0.00141	0.00447	0.02516	0.03209	0.04241	0.72834	0.11509	0.04566	0.00525	0.00000
	7	0.00001	0.00016	0.00052	0.00260	0.00730	0.00419	0.12198	0.68147	0.16283	0.01895	0.00000
	8	0.00000	0.00001	0.00004	0.00030	0.00057	0.00053	0.01885	0.05747	0.86099	0.06124	0.00000
	9	0.00000	0.00000	0.00000	0.00002	0.00004	0.00004	0.00178	0.00596	0.17091	0.82124	0.00000
	10	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	1.00000

Table 47: Natural history transition matrix based on information from the British Columbia dataset (above median age)

EDSS from/to		EDSS state (to)										
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
EDSS state (from)	**0**	0.69537	0.20294	0.07251	0.02170	0.00422	0.00137	0.00175	0.00011	0.00003	0.00000	0.00000
	1	0.05826	0.69503	0.15781	0.06087	0.01638	0.00458	0.00643	0.00048	0.00013	0.00001	0.00000
	2	0.01586	0.12135	0.60786	0.16796	0.04458	0.01849	0.02160	0.00174	0.00052	0.00004	0.00000
	3	0.00594	0.04961	0.12008	0.54421	0.09107	0.05844	0.11651	0.01029	0.00355	0.00030	0.00000
	4	0.00165	0.02214	0.06660	0.11518	0.48936	0.10387	0.16812	0.02580	0.00671	0.00056	0.00000
	5	0.00052	0.00533	0.02942	0.05866	0.08738	0.48692	0.27312	0.03880	0.01883	0.00102	0.00000
	6	0.00012	0.00133	0.00444	0.02497	0.03069	0.04080	0.74072	0.10894	0.04377	0.00423	0.00000
	7	0.00001	0.00015	0.00052	0.00247	0.00727	0.00385	0.11683	0.69268	0.16063	0.01559	0.00000
	8	0.00000	0.00001	0.00004	0.00029	0.00055	0.00050	0.01880	0.05573	0.90340	0.02067	0.00000
	9	0.00000	0.00000	0.00000	0.00002	0.00004	0.00003	0.00176	0.00568	0.17414	0.81832	0.00000
	10	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	1.00000

14.2.4 Types of multiple sclerosis

The model includes people who commenced in an RRMS health state and progressed to SPMS. People with CIS, primary progressive multiple sclerosis or benign disease were not included in the analysis.

14.2.5 Interventions

The interventions considered in the economic analyses are presented in Table 48. The interventions included IFN β-1a 30 µg IM once weekly (Avonex), IFN β-1a 44 or 22 µg SC three times weekly (Rebif), IFN β-1b 250 µg SC every other day (Betaferon/Extavia), pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy) and GA 20 mg SC daily or 40 mg SC three times weekly (Copaxone), as well as fingolimod (Gilenya), natalizumab (Tysabri) and dimethyl fumarate (Tecifdera) as second-line therapies. It is assumed that the split between these second-line therapies will be 50%, 30% and 20% respectively, based on expert opinion. The interventions are compared against best supportive care treatment for people with RRMS.

Table 48: Interventions included in the economic analysis, Teva model

Brand	Drug	Dose regime	Route of administration	Label indications
Avonex	IFN β-1a	30 µg once a week	Intramuscular	RRMS
Rebif		RRMS: 22 or 44 µg three times per week	Subcutaneous	RRMS
Betaferon/Extavia	IFN β-1b	300µg every other day		RRMS
Plegridy	Pegylated IFN β-1a	250µg every 2 weeks		RRMS
Copaxone	Glatiramer acetate	20mg once daily	Oral	RRMS
Gilenya	Fingolimod	500mg once daily	Oral	RRMS
Tysabri	Natalizumab	300mg once every 4 weeks	IVI	RRMS
Tecfidera	Dimethyl fumarate	240mg twice daily	oral	RRMS
IFN, interferon; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; IVI, Intravenous infusion.				

14.2.6 Model structure

The illustrative Markov model structure submitted by the company was based on the original ScHARR model[257] with developments to include other interventions. The company used a cohort-based Markov model to depict the natural history of people with RRMS. The model simulated the disability progression, progression from RRMS to SPMS, and the relapsing nature of the disease. People with RRMS were able to occupy one of the EDSS health states, which ranged from 0 to 10, and in increments of 0.5. The model allowed for people to progress, regress or stay in the same EDSS health state, or progress from EDSS to SPMS. When people progress to SPMS, they can progress, regress or remain in the same EDSS state.

In the model, people incurred costs and accrued benefits depending on the EDSS state for RRMS and SPMS. Benefits were measured using quality-adjusted life years, whereby each model cycle a utility is assigned to people occupying a specific health state.

14.2.7 Population

The population included in the economic analysis was similar to the population for the RSS dataset (i.e. [redacted] of females with a starting age of 30 years with relapsing-remitting multiple sclerosis). The initial distribution of people in each EDSS state is presented in Table 49.

Table 49: Baseline distribution of people by EDSS score, Teva model

EDSS	Distribution (%)
0	3%
1	16%
2	26%
3	23%
4	16%
5	10%
6	6%
7	0%
8	0%
9	0%
10	0%

14.2.8 Resource use and costs

All costs included in the analysis were those directly related to the NHS and PSS perspective, and were reported in pounds sterling in 2015/16 prices. The model included the following resource use and costs in order to conduct their analyses:

- Drug acquisition costs
- Administration costs
- Monitoring costs
- Health state/EDSS costs
- Cost of relapse
- Treatment-related adverse event costs

14.2.9 Drug acquisition costs

Treatment costs for glatiramer acetate (Copaxone) along with the other DMTs are presented in Table 50. Annual costs were presented for the list and net price for each DMT that was available at the time of the RSS. From the Excel model submitted, cost of treatments were based on the dosage (per week and year), price per packet, and the annual costs for each drug was derived.

Table 50: Annual treatment costs, Teva model

DMT	Annual acquisition costs (list price: £, 2014/15 prices)	Annual acquisition costs (net price: £, 2014/15 prices)
Glatiramer acetate (Copaxone)	6,704.29	[redacted]
IFN β-1a 30 µg IM weekly (Avonex)	8,531.20	8,501.98
IFN β-1b 250 µg SC every other day (Betaferon)	7,264.82	7,259.34

IFN β-1a 44 µg SC three times weekly (Rebif)	10,608.43	[redacted]
IFN β-1a 22 µg SC three times weekly (Rebif)	8,003.67	[redacted]
Fingolimod (Gilenya)	19,175.63	19,175.63
Natalizumab (Tysabri)	14,740.45	14,740.45
Dimethly fumarate (Tecfidera)	17,910.29	[redacted]
Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)	8,531.20	8,531.20

Where no net prices for DMTs were available because of treatments not being included in the RSS, the list price of these drugs were used in the analysis.

14.2.10 Administration costs

Annual administration costs included costs associated with training/teaching people self-administration. The administration costs are presented in Table 51.

Table 51: DMT administration costs, Teva model

DMT	Annual administration cost for Year one (£, 2014/15)	Resource use	Annual administration cost for subsequent years (£, 2014/15)	Resource use
Glatiramer acetate (Copaxone)	174.00	3 hours of nurse's time to teach self-administration	0.00	None
IFN β-1a 30 µg IM weekly (Avonex)				
IFN β-1b 250 µg SC every other day (Betaferon/Extavia)				
IFN β-1a 44 µg SC three times weekly (Rebif)				
IFN β-1a 22 µg SC three times weekly (Rebif)				
Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)				
Fingolimod (Gilenya)	144.99	Continuous electrocardiogram and blood presume monitoring for six hours following first dose	0.00	None
Natalizumab (Tysabri)	5,199.02	Thirteen infusions per year with 1g Methylprednisolone per infusion	5,199.02	Thirteen infusions per year with 1g Methylprednisolone per infusion
Dimethyl fumarate (Tecfidera)	0	None	0	None

14.2.11 Monitoring costs

Annual monitoring costs for each treatment were presented in Appendix 6 of the main report. The company clearly outlined the resource use, used to derive monitoring costs. Monitoring costs were presented for Year one and for subsequent years. The monitoring costs for all interventions are presented in Table 52. These annual monitoring costs appeared to be derived and used in the model correctly. The monitoring costs for second line therapies are not presented in appendix 6 of the submission.

Table 52: Annual monitoring costs for each DMT, Teva model

DMT	Monitoring costs for Year 1 (£, 2014/15)	Monitoring costs for subsequent years (£, 2014/15)
Glatiramer acetate (Copaxone)	414.00	414.00
IFN β-1a 30 µg IM weekly (Avonex)	521.08	512.54
IFN β-1a 22 µg SC three times weekly (Rebif)	521.08	512.54
IFN β-1a 44 µg SC three times weekly (Rebif)	521.08	512.54
Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)	521.08	512.54
IFN β-1b 250 µg SC every other day (Betaferon/Extavia)	521.08	512.54

14.2.12 Health state/EDSS costs

Health state costs (payers' perspective) by EDSS level and type (RRMS/SPMS) are presented in Table 53. These costs were related to MS management (expected/unexpected visits to healthcare providers). The costs were taken from the ScHARR model and inflated to 2015 prices. Sensitivity analyses were carried out using health state costs sourced from Tyas et al.[268] and from Karampampa et al.[264] The former involve lower costs for high EDSS scores, and increase the ICER for glatiramer acetate (Copaxone) to [redacted].

Table 53: Mean unit costs from payers' perspectives, Teva model

EDSS State	0	1	2	3	4	5	6	7	8	9
Cost (£)	1,195	1,195	1,195	2,204	2,284	8,049	8,978	27,398	42,541	54,080

14.2.13 Cost of relapse

The cost of a mild relapse was estimated at £870, and the cost of a severe relapse requiring hospitalisation was £5,580. The submission states that these costs were sourced from the manufacturer submission for NICE TA312[269] (alemtuzumab for treating RRMS), which took these costs from a budget impact analysis in the republic of Ireland (Dee 2012).[270]. This raises questions about the robustness of the estimate, and its relevance for a UK setting. The assessment group for TA312 conducted their own sensitivity analysis in which the cost of

a severe relapse was assumed to be lower (£3039). A justification for this was not presented in the report, but it implies that the assessment group at the time thought the higher figure might be an overestimate.

14.2.14 Cost of adverse events

The model included costs for adverse events as a result of disease modifying treatment. In Appendix 6 of the company's submission, estimates on resource use have been presented. Table 54 shows the annual costs of treatment for adverse events used in the model by DMT. Unit costs for resources used to manage adverse events were sourced from the PSSRU,[260] national reference costs and the manufacturer submission for TA312[269], although insufficient detail is presented for the accuracy of the costs assumed for adverse events to be fully verified.

Table 54: Annual cost of treatment for adverse events by DMT, Teva model

DMT	Unit cost (£, 2014/15)	Unit cost (£, 2014/15)
	Year 1	Year 2
Glatiramer acetate (Copaxone)	44.61	44.61
IFN β-1a 30 µg IM weekly (Avonex)	32.81	32.81
IFN β-1a 22 µg SC three times weekly (Rebif)	20.59	20.59
IFN β-1a 44 µg SC three times weekly (Rebif)	26.90	26.90
Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)	13.64	22.66
IFN β-1b 250 µg SC every other day (Betaferon/Extavia)	30.75	30.75
IFN, interferon; IM, intramuscular; SC, subcutaneous		

14.2.15 Health state utility values

Utilities were derived by EDSS level and assumed to be independent of MS type (RRMS and SPMS). In the base case, these were derived from the same sources as the RSS model. Utility values used in the model are presented in Table 55.

Table 55: Utility values by health state, Teva model

EDSS State	0	1	2	3	4	5	6	7	8	9
Utility	0.925	0.761	0.674	0.564	0.564	0.491	0.445	0.269	0.008	-0.230
Carer's disutilities	0.002	0.002	0.002	0.002	0.045	0.142	0.167	0.063	0.095	0.095

14.2.16 Carer's disutility

An analysis was undertaken which included carers' disutilities by EDSS state. Table 55 shows the disutility values used in the model.

14.2.17 Mortality rate

An EDSS-dependent mortality multiplier was used to estimate mortality from UK general population rates (sourced from ONS data for 2012-2014). These multipliers were taken from the Teriflunomide manufacturer submission to NICE (which were themselves adapted from Pokorski et al. (1997).[271, 272] This raises concerns around the robustness of assumed mortality, and questions around whether a more up to date source could be identified.

14.2.18 Adverse event disutility

The assumed annual disutilities due to adverse events are given in Table 56. These were calculated from adverse event rates derived from clinical trials of the treatments included in the submission. Disutilities for adverse events were obtained from Maruszczak et al.[267] and from manufacturer submissions to NICE for alemtuzumab, teriflunomide, dimethyl fumarate, and IFN β-1a 44 µg SC three times weekly (Rebif).

Table 56: Disutilities associated with adverse events, Teva model

Disease modifying treatment	Annual adverse event disutility	
	Year 1	Year 2+
Glatiramer acetate (Copaxone)	-0.0043	-0.0043
IFN β-1a 30 µg IM weekly (Avonex)	-0.0009	-0.0009
IFN β-1a 22 µg SC three times weekly (Rebif)	-0.0027	-0.0027
IFN β-1a 44 µg SC three times weekly (Rebif)	-0.0034	-0.0034
Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)	-0.0043	-0.0037
IFN β-1b 250 µg SC every other day (Betaferon/Extavia)	-0.0028	-0.0028

14.2.19 Relapse

The disutility per relapse was assumed to be 0.058 QALYs if the relapse was severe, and 0.009 otherwise. The lower utility was based on the study by Orme et al.[105] The manufacturer was unable to identify a UK source for estimating disutility associated with severe relapse. Estimates for a US population were identified, but the manufacturer argues that these over-estimate the equivalent for a UK population. They therefore downweighted this utility by the ratio of UK to US disutilities for non-severe relapse (0.071/0.091), which resulted in a reduction of the severe disutility from 0.302 to 0.236. This was combined with an assumed duration of 90 days to give the 0.058 estimate.

14.2.20 Treatment discontinuation

In the Teva model, people who progressed to an SPMS health state discontinued treatment. Accordingly, treatment was assumed to discontinue at EDSS state 7, in agreement with ABN guidelines.[262]

14.2.21 Analysis (cycle length, time horizon and perspective)

The analysis was undertaken from the NHS and Personal Social Services (PSS) perspective. The outcome measure used in the analysis was QALYs gained, over a 50-year time horizon with annual cycle lengths. The starting age of the population was 30 years. Results were presented as an incremental cost-effectiveness ratio (ICER) and expressed as cost per QALYs gained. Both costs and benefits were discounted at 3.5% per annum.

14.2.22 Summary of model assumptions

In summary, the Teva model made the following assumptions:

1. The probability of transitioning to a health state in the subsequent cycle depends only on the health state in the present cycle
2. Transition from RRMS to SPMS is accompanied by an increase in EDSS scale of 1
3. Each year, EDSS score can remain the same, increase or decrease
4. In the base case, treatments affect EDSS progression but not EDSS regression
5. Treatment effects on relapse and EDSS progression are independent
6. In the base case, treatments have the same effect on progression in each EDSS state
7. In the base case, treatment efficacy is constant over time
8. Treatments do not directly impact transitions to SPMS, but impact patients' EDSS state, which influences transition to SPMS
9. Treatment discontinuation is constant for all years
10. The annualised adverse event risks are applied every year - this may overestimate the incidence of adverse events since patients who have adverse events may discontinue in the initial years on treatment
11. Patients who discontinue move on to one of three second-line treatments – Gilenya (50%), Tysabri (30%) and Tecfidera (20%)
12. SPMS patients receive BSC only
13. Patient access schemes for which data are publicly available are considered in the base case

14.2.23 Summary of results

Base-case results showed that treatment with glatiramer acetate (Copaxone) resulted in a mean gain per patient of [redacted] life years or [redacted], at a net discounted cost of [redacted], giving an ICER of [redacted] per QALY. The probability of cost-effectiveness for glatiramer acetate (Copaxone) copaxone relative to best supportive care was [redacted] at £20,000 per QALY and [redacted] at £30,000 per QALY.

14.3 Merck

14.3.1 Background

This section of the report focuses on the economic evidence submitted by Merck Biopharma on IFN β-1a 44 µg/22 µg SC three times weekly (Rebif). In the section, we will provide a summary of the economic analysis presented by Merck, and then critically appraise their analysis and findings. Merck have provided NICE with their economic model and analysis of IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) for the treatment of RRMS, SPMS and CIS; this includes details on the intervention and comparators, study population, resource use and costs, the modelling methodology, and assumptions.

In the Merck IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) model, an economic analysis was conducted to assess the costs-effectiveness of this DMT compared with best supportive care for people with RRMS, SPMS and CIS. Merck initially conducted a systematic review of the cost-effectiveness literature relating to MS and identified four studies that meet their inclusion criteria, two of these studies examined DMTs in CIS. In addition, they reviewed cost-effectiveness analysis undertaken as part of health technology assessments for NICE (4

publications) and CADTH (1 publication). The concluded that majority of studies used a comparable approach to the ScHARR analysis[257] undertaken for TA32. In addition, they highlight that they adopted a commonly used approach to modelling mortality for MS patients, although they have not specified which studies from their review used this approach.

14.3.2 Merck IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) RRMS model

For the RRMS model analysis, a Markov model was used to depict the natural history of people with RRMS. The analysis was undertaken from the UK National Health Service (NHS) and Personal and Social Services (PSS) perspective. The outcome measure used in the analysis was quality-adjusted life-years (QALYs). The model was run over a 50-year time horizon with one-year cycles and half-cycle correction was applied. A 3.5% discount rate was applied to all future costs and health outcomes.

The model used EDSS scores, increasing increments of one, to model disability progression with and without DMDs. The model does not have separate health states for SPMS and assumes all patients stop DMTs upon reaching EDSS 7. The British Columbia natural history model[151] was used to model disease progression in people with RRMS. For those not on treatment, disability could improve (backward transition in EDSS scores). The model included information from both doses of the drug; thus they estimated outcomes for patients given both doses, based on numbers given the respective doses in the RSS cohort, and then pooled the outcomes. Of note, the model used dose specific parameters to populate their models (e.g. costs, treatment effects etc.)

In their analysis, the initial distribution of EDSS scores were based on what was observed in the RSS IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) treated dataset. Treatment effects were assumed to delay the progression of the disease and reduce the frequency of relapses. For progression, they used the hazard ratios from the 10-year RSS data provided by DH to model the impact of DMTs on disability progression (worsening EDSS scores). They also incorporated the 'waning effect' of DMTs on disability progression hazards. For relapse rates, they used findings from the PRISMS study.[187] In their base case analysis, they modelled mortality in the same way as the ScHARR model[257] by applying a SMR of 2.0 to life table mortality estimates, and an additional MS-specific mortality risk applied to those whose EDSS scores reaches 6.

Health outcomes were measured in QALYs. For this they assigned utility weights to the EDSS health states and included utility decrements for caregivers, relapses and adverse drug reactions. Utility estimates were derived by pooling data from the UK MS Trust postal survey, as cited in the company submission, and the Heron dataset.[105] The data were pooled using sample size weighted averages, and undertaken by IMS Health for the MS trust. They assumed the duration of the utility decrement from a relapse to be 46 days, and approximately 5% per annum would experience utility decrement from an adverse event. Healthcare resource use and cost estimates used in the model were derived from the DH/ScHARR estimates[257] and adjusted accordingly. The costs were assigned to EDSS health states, and for relapses. The cost of DMTs was based on the annual per-patient NHS acquisition cost.

Merck undertook a number of sensitivity analyses to investigate the impact of discounting, shorter time horizons, alternative approaches to deriving mortality rates and hazard ratios, alternative sources for utility and costs, alternative assumptions regarding adverse events and discontinuation rates. In addition, they undertook probabilistic sensitivity analysis to determine the robustness of the base-case results.

In their base case analysis, they estimated that treatment of RRMS with IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) would result in an additional [redacted] QALYs gained at an additional cost of [redacted] over a 50-year time horizon. They estimated the ICER to be [redacted]/QALY gained. The ICER estimated from the PSA was [redacted]/QALY gained. In their sensitivity analysis, they found the base-case results were robust to univariate changes made to key input parameters. The majority of their sensitivity analyses resulted in the ICERs being lower. The ICERs were higher when they used different approaches to estimate EDSS health state costs.

14.3.3 Merck IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) SPMS model

Merck also undertook an economic analysis of providing IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) (Rebif) to patients with SPMS. The used the same model structure and modelling techniques as before, and populated the model with patient characteristics and treatment effects for treatment with IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) in SPMS patients. As highlighted before, the model does not include separate health states for SPMS and assumed all patients stop DMTs upon reaching EDSS 7. For the characteristics of the population modelled they used observed data from the SPECTRIMS study,[222] and assumed 64% female, mean age 43 years and patients had EDSS score 5 or 6 at baseline. Additional assumptions they made included the constant relapse rate independent of EDSS level.

In their base-case deterministic analysis, they estimated that treatment of SPMS with IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) would result in an additional [redacted] QALYs gained at an additional cost of [redacted] over a 50-year time horizon. They estimated the ICER to be [redacted]/QALY gained. The ICER estimated from the PSA was [redacted]/QALY gained. In their sensitivity analysis, they found the base-case results were robust to univariate changes made to key input parameters. The majority of their sensitivity analyses resulted in comparable ICER estimates (Appendix 17 of company submission).

14.3.4 Merck IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) CIS model

Merck also undertook an economic analysis of providing IFN beta-1a (Rebif) to patients with CIS. They estimated the ICERs for starting DMDs in CIS patients, to providing best supportive care for CIS patients with DMDs when patients progress to RRMS. The used the same model structure and modelling techniques as before, and populated the model with patient characteristics and treatment effects for treatment with IFN beta-1a (Rebif) in CIS patients. The characteristics of population modelled were based on participants of the REFLEX study.[173] The relative risks for conversion from CIS to RRMS for the first and second year on DMTs, and relative risk of relapse were extracted from the REFLEX study. In addition, they assumed there was no treatment effect of DMTs on risk of progression to RRMS after two years. For delayed therapy we considered that the rate of conversion and relapse were also based on the placebo arm of the REFLEX study, although this is not clear from thr submission. They also assumed that for CIS patients EDSS scores remained constant till conversion to RRMS, at which point the EDSS score was based on the EDSS score whilst in the CIS state.

In their base-case deterministic analysis, they estimated that early treatment of CIS with IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) would result in an additional [redacted] QALYs gained at an additional cost of [redacted] over a 50-year time horizon. They estimated the ICER to be [redacted]/QALY gained. The ICER estimated from the PSA was [redacted]/QALY gained. In their sensitivity analysis, they found the base-case results were robust to

univariate changes made to key input parameters. The majority of their sensitivity analyses resulted in comparable ICER estimates (Appendix 17 of company submission).

14.3.5 Evaluation of Merck's IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) submission

Types of multiple sclerosis

Merck undertook economic analysis of IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) for treatment of RRMS, SPMS and CIS. The base case analysis examined costs and health outcomes for MS patients aged<30.

Model structure

The illustrative Markov model structure submitted by the company was based on the original School of Health and Related Research (ScHARR) model.[257] The company used a cohort-based Markov model to depict the natural history of people with RRMS. The model simulated the disability progression, progression from RRMS to SPMS, and the relapsing nature of the disease. People with RRMS/SPSS were able to occupy one of the EDSS health states, which ranged from 0 to 9, and in increments of 1.0. The model allowed for people to progress, regress or stay in the same EDSS health state, or progress from EDSS to SPMS. For those on DMDs no backward transition in EDSS score was permitted.

They used the same model structure for the economic analysis of DMTs for treatment of SPMS, and parameterised the model with patient characteristics and treatment effects for treatment with IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) in SPMS patients. The CIS model had an additional 5 on treatment and 5 off treatment health states defined by EDSS score (0-5, increments of one) for CIS. In addition, for the CIS model they assumed that EDSS scores remained constant till conversion to RRMS, at which point the EDSS score was based on the EDSS score whilst in the CIS state.

Interventions

The interventions considered in the economic analyses are presented in Table 57. For RRMS they compared IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) to best supportive care, for SPMS they compared IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) to best supportive care, and for CIS they compared IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) to best supportive care for CIS with DMTs started on progression to RRMS. For all those started on DMTs, treatment was discontinued once EDSS score ≥7 and 5% per annum discontinued treatment due to adverse reactions. For DMT treatment strategy, the model aggregated the observed RSS data across both doses of the drug.

Table 57: Interventions included in the economic analysis, Merck model

Brand	Drug	Dose	Route of Administration	Type of MS
Rebif	IFNβ-1a	44 µg or 22 µg	Subcutaneous	RRMS
	IFNβ-1a	44 µg or 22 µg	Subcutaneous	SPMS
	IFNβ-1a	44 µg or 22 µg	Subcutaneous	CIS
CIS, clinically isolated syndrome; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis				

Population

For their RRMS model, the population included in the economic analysis was similar to the population who started IFN beta-1a (Rebif) in the RSS cohort. In their base case RRMS analysis they examined the costs and health outcomes for MS patients aged<30. In addition, they examined costs and health outcomes for MS patients aged ≥30. For their SPMS model, the population included in the economic analysis was similar to the population included in the SPECTRIMS study,[222] and for CIS, the population included in the REFLEX study.[173] The initial distribution of people in each EDSS state is presented in Table 58. Of note, the distribution of initial EDSS scores for the RRMS population below were taken from the Excel file and are not the same as that presented in the company's final written summary.

Table 58: Baseline distribution of people in the base case analysis, Merck model

	Population	EDSS score						
		0	1	2	3	4	5	6
RRMS: 44µg < 30 years	[redacted] Female Mean age of onset: 30 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RRMS: 22µg < 30 years		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SPMS (all)	64.0% Female Mean age of onset: 43 years	0%	0%	0%	0%	0%	50%	50%
CIS	67.0% Female Mean age of onset: 31 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CIS, clinically isolated syndrome; EDSS, expanded disability scale score; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis								

Mortality rate

In their base-case analysis, the company modelled mortality in the same way as the ScHARR model by applying an SMR of 2.0 to life table mortality estimates, and an additional MS-specific mortality risk applied to those whose EDSS scores reaches 6. In their sensitivity analyses they used an alternative approach to modelling mortality. Briefly, this approach resulted in lower mortality rates assigned to early EDSS health states, and higher mortality rates from those with more advanced disability. Whilst this approach may be valid, the data used to derive these values is from about 20 years ago, when best supportive care is likely to have been less optimal than current provision, especially for those with more advanced disability.

Treatment effects of disease modifying treatments

Merck followed the same approach used in the DH RSS model analysis in modelling the impact of DMTs on disability progression. The British Columbia natural history model[151] was used to model disease progression in people with RRMS, allowing for improvements in disability (backward transition in EDSS scores).

For their RRMS model, the DMT strategy utilised the IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) specific hazard ratios supplied by the DH from the year 10 RSS data. These hazard ratios were applied to the natural history model to model the on treatment impact. Of note, they individually modelled the treatment impact

for the two different dosages of the drug, and pooled the final costs and health outcomes to estimate the ICERs. They also assumed that there would be no improvement in disability (backward transition in EDSS score) for those on DMTs. In their models they assumed that IFN β-1a 44 μg/22 μg SC three times weekly (Rebif) would be stopped when disability progressed to EDSS level ≥7. In addition, they assumed that 5% of patients stopped treatment for other reasons (i.e. drop out) every year. They also incorporated the 'waning effect' of DMTs on disability progression hazards. For relapse rates they used findings from the PRISMS study.

In the CIS model, progression to RRMS in the delayed treatment strategy (DMTs once progressed to RRMS), and the rate of conversion and relapse were based on the outcomes of placebo arm of the REFLEX study.[173] For the DMT CIS treatment strategy the relative risks for conversion from CIS to RRMS for the first and second year on DMTs, and relative risk of relapse were extracted from the REFLEX study. The company assumed that there was no treatment effect of DMTs on risk of progression to RRMS after two years. They also assumed that for CIS patients EDSS scores remained constant till conversion to RRMS, at which point the EDSS score was based on the EDSS score whilst in the CIS state.

Resource use and costs

All costs included in the analysis were those directly related to the NHS and PSS perspective, and were reported in 2015 UK pounds sterling, with future costs discounted at a rate of 3.5% per annum. The model included the following resource use and costs in order to conduct their analyses:

- Drug acquisition costs
- Health state/EDSS costs
- Cost of relapse
- Adverse event costs

Drug acquisition costs

In their model, the drug acquisition costs represents the annual per-patient NHS acquisition cost [redacted]. The drug acquisition costs for the two dosages of IFN β-1a SC three times weekly (Rebif), 44 μg and 22 μg, were [redacted] and [redacted] respectively. In their model they utilized the observed numbers on the two different dosages in the RSS cohort and assigned costs accordingly. Hence the true-modeled cost of the drugs will be an RSS sample weighted average. The costs of administering the drugs and monitoring response to treatment have not been included.

Health state/EDSS costs

Resource use/costs were assigned to each EDSS health state. In the base case analysis they utilised the same costs as previously used in the ScHARR analysis[257] with adjustment to 2015 UK pounds. This is the same approach used in the DoH RSS model analysis. In their sensitivity analysis they did estimate the ICER using costs reported by Tyas et al (2007)[268] and Karampampa et al (2012),[264] again with adjustment to 2015 UK pounds.

Cost of relapse

In the base-case analysis the company utilised the same costs as previously used in the ScHARR analysis with adjustment to 2015 UK pounds. This is the same approach used in the DoH RSS model analysis.

Adverse event costs

In the base-case analysis the company did not include costs incurred as a result of adverse reactions, in accordance with the DoH RSS model analysis. They undertook sensitivity analysis and incorporated costs incurred as a result from adverse events. For this they used data on adverse events reported in the PRISMS study.[187]

Health state utility values

Health outcomes were measured in QALYs and future health outcomes were discounted at a rate of 3.5% per annum. Utility weights were assigned to the EDSS health states, including utility decrements for caregivers, relapses and adverse drug reactions. Utility estimates were derived by pooling data from the UK MS Trust postal survey and the Heron dataset. The data was pooled using sample size weighted averages, and undertaken by IMS Health for the MS trust. They assumed the duration of the utility decrement from a relapse to be 46 days, and approximately 5% per annum would experience utility decrement from an adverse event.

Table 59 shows the utility weights used in their base-case analysis. Of note, the pooled values do not take into account differences between the two samples in terms of age, sex and other variables that may be independently associated with HRQoL. The pooled utility values are the ones that were used in the DH RSS model analysis, including the impact on caregivers. They state that as the pooled values were not provided with standard errors for the PSA, they therefore used the standard errors reported in one of the two datasets that were pooled (Orme et al).[105] For this they extracted the standard errors from the multivariable regression analysis, and therefore represent the standard errors for the adjusted coefficients.

In their sensitivity analysis they estimated the ICERs utilising different utility weights. They estimated the ICER using utility values derived from an unpublished study by Boggild, and using utility values derived from pooling all three datasets (unpublished data from UK MS Trust postal survey; Heron dataset;[105] unpublished data from Boggild et al.). The utility values assigned to health states in their sensitivity analysis were lower (poorer HRQoL).

Table 59: Summary of utility values for the base case analysis, Merck model

State	Utility value: mean (standard error)	
	Patient health states	Caregiver decrements
EDSS 0	0.925 (0.045)	-0.002 (0.053)
EDSS 1	0.761 (0.048)	-0.002 (0.053)
EDSS 2	0.674 (0.048)	-0.045 (0.057)
EDSS 3	0.564 (0.052)	-0.045 (0.057)
EDSS 4	0.564 (0.048)	-0.142 (0.062)
EDSS 5	0.491 (0.047)	-0.16 (0.055)
EDSS 6	0.445 (0.047)	-0.173 (0.054)
EDSS 7	0.269 (0.049)	-0.03 (0.038)
EDSS 8	0.008 (0.050)	-0.095 (0.075)
EDSS 9	-0.23 (0.074)	0
Relapse	-0.22 (0.089) for 46 (10) days	
Adverse effect	-0.321 (0.051) in 5.1% (8.6%) patients	

14.3.6 Analysis (cycle length, time horizon and perspective)

The analysis was undertaken from the National Health Service (NHS) and Personal Social Services (PSS) perspective. The outcome measure used in the analysis was quality-adjusted life-years gained, over a 50-year time horizon with annual cycle lengths. Results were presented as an incremental cost-effectiveness ratio (ICER) and expressed as cost per quality-adjusted life-years (QALYs) gained. Both costs and benefits were discounted at 3.5% per annum

14.3.7 Assumptions

Merck made a range of assumption in the model analysis. For their RRMS model they assumed:

1. The Year 10 RSS dataset reflects the future MS population characteristics, initial EDSS level on starting DMTs, dosage of IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) and treatment impact on disability progression.
2. Age of MS diagnosis was assumed to be 30 years.
3. Natural history progression of MS, resource use, HRQoL, waning effect of DMTs, and mortality rates were the same as that used by the UK Department of Health in their RSS model analysis.
4. Uncertainty around the hazard ratios characterising treatment impact of DMTs was assumed to have as an upper limit 1.0 in the PSA.
5. DMTs were discontinued once EDSS level reached 7.
6. 5% of patients discontinue DMTs for other reasons (dropout).

The model included additional assumptions relating to SPMS.

1. Starting EDSS 5 and 6 (50% each)
2. Untreated relapse rate set at 1.08 per patient year.
3. Hazard ratios for progression and relative risks for relapse were used per the SPECTRIMS[222] relapsing population.

Finally, the model included several assumptions relating to CIS.

1. Patients' baseline EDSS is as in REFLEX.[173]
2. Conversion from CIS is as in REFLEX for delayed treatment, with relative risks for years one and two calculated from REFLEX.
3. No treatment effect is applied beyond year two, though patients are assumed to remain on treatment for up to 5 years with CIS.
4. Patients are assumed to remain in the starting EDSS during and upon conversion to McDonald MS.

14.3.8 Summary of results

In their base-case analysis, Merck estimated that treatment of RRMS with IFN β-1a 44 µg/22 µg SC three times weekly (Rebif) would result in an additional [redacted] QALYs gained at an additional cost of [redacted] over a 50-year time horizon. They estimated the ICER to be [redacted] QALY gained. The ICER estimated from the PSA was [redacted]/QALY gained.

Table 60: Summary of economic evaluations undertaken by companies

Parameter	Company and drug		
	Biogen: IFN β-1a 30 µg IM once weekly (Avonex), pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy)	**Merck: IFN β-1a 44 or 22 µg SC three times weekly (Rebif)**	**Teva: Glatiramer acetate 20 mg SC daily or 40 mg three times weekly (Copaxone)**
Natural history cohort	Natural history cohort based on extrapolating the ADVANCE placebo arm data with British Columbia cohort	Natural history cohort based on British Colombia natural history model.	Natural history cohort based on London Ontario natural history cohort
Population	Adults (≥ 18 years) with RRMS	RRMS Adults: Mean age 30 years; [redacted] female. Based on RSS data SPMS Adults: Mean age 43 years; 64% female. Based on SPECTRIMS CIS Adults: Mean age 31 years; 67% female. Based on REFLEX	Adults (≥ 18 years) with RRMS
Intervention	**Avonex** IM IFN β-1a 30µg IM once weekly **Plegridy** Pegylated INFβ-1a 125µg SC every two weeks **Rebif** IFN β-1a 44µg SC three times weekly **Betaferon** SC INFβ-1b 250µg every other day **Extavia** SC INFβ-1b 250µg every other day **Copaxone** GA 20mg once daily	**Rebif** SC INFβ-1a 44µg or 22µg three times weekly.	**Copaxone** GA 20mg once daily **Avonex** IM IFNβ-1a 30µg once weekly **Plegridy** SC pegINFβ-1a 250µg every two weeks **Rebif** SC INFβ-1a 22µg three times weekly **Rebif** SC INFβ-1a 44µg three times weekly **Betaferon** SC INFβ-1b 300µg every other day **Gilenya**

	Copaxone GA 40mg once daily		500mg once daily **Tysabri** 300mg once every 4 weeks **Tecfidera** 240mg twice daily
Comparator	Best supportive care	CIS: Best supportive care for CIS and DMDs for RRMS RRMS: Best supportive care SPMS: Best supportive care	Best supportive care
Type of model and health states	Cohort based Markov model with 21 health states (10 for RRMS, 10 for SPMS and dead the dead state) characterised by EDSS levels, which ranged from 0-10 with increments of 0.5	CIS Cohort based Markov model with an additional 5 on treatment and 5 off treatment health states for CIS defined by EDSS score (0-5, increments of one) for CIS. Otherwise includes same health states as for RRMS model RRMS + SPMS Cohort based Markov model with 21 health states: 10 EDSS not on treatment states; 10 EDSS on treatment states; absorbing death state. EDSS health states 0-9, with increments of 1.0	Cohort based Markov model with 21 health states (10 for RRMS, 10 for SPMS and one for the dead state) characterised by EDSS levels, which ranged from 0-10 with increments of 1
Hazard ratio	Hazard ratios based on confirmed disability progression. The year 10 implied hazard ratio of [redacted] for IM IFNβ-1a 30µg was used in the company's model	CIS Conversion rate for CIS to RRMS based on REFLEX study RRMS Hazard ratios for sustained disability progression supplied to	Hazard ratios for Copaxone of [redacted] for disability progression and [redacted] derived from 10 year RSS. Sensitivity analysis based on manuf NWMA assuming [redacted] HR for progression vs BSC.

		Merck by the DH based on analysis of year 10 RSS data. **Progression** [redacted] **Relapse** HR (44µg): 0.67 HR (22µg): 0.71 SPSMS Relapse rate for SPMS not on treatment based on placebo arm of SPECTRIMS. HR for treatment derived from SPECTRIM, but utilised HR for 44 µg dosage as lack of confidence intervals for 22µg dosage. **Progression** HR (44µg): [redacted] **Relapse** HR (44µg): 0.62 HR (22µg): 0.53	
Resource use and costs	Drug acquisition costs, monitoring costs, administration costs, relapse costs (including a percentage requiring hospitalization as a proxy for severity), health state costs, treatment-related adverse event costs	RRMS Based on DH/ScHARR resource use and costs, adjusted to 2015. Costs include grug acquisition costs, monitoring costs, administration costs, relapse costs, health state costs, treatment-related adverse event costs SPMS and CIS Based on RRMS model approach	Drug acquisition costs, monitoring costs, administration costs, relapse costs (including a percentage requiring hospitalization as a proxy for severity), health state costs, treatment-related adverse event costs

Health-related quality of life	Utility values by EDSS level were based on information from the ADVANCE trial and Orme et al., 2007, which were derived from utility values from the UK MS survey Carers' disutilities were derived based on information obtained from the manufacturer's submission to NICE for TA127.	Utility values by EDSS score Utility values derived by pooling data from a UK MS Trust postal survey and the Heron dataset. Data pooled using sample size weighted averages, and undertaken by IMS Health for the MS trust.	Utility values by EDSS level were based on information from Orme et al., 2007, which was derived from utility values from the UK MS survey. A sensitivity analysis was performed using smoothed data from three RSS datasets. Carers' disutilities were derived based on information obtained from the manufacturer's submission to NICE for TA127.
Discontinuation of treatment	Only people who progressed to secondary progressive multiple sclerosis discontinued disease modifying treatment	Treatment is stopped when EDSS score reaches 7. In addition, 5% stop treatment irrespective of EDSS levels. Derived from observed drop-out rate from the 8-year RSS data.	Withdrawal rate of 5% per year as per RSS model. Treatment also discontinued for EDSS 7+
Relapse	Relative risk of a relapse per person in the RRMS health states has been estimated from the ADVANCE study for EDSS levels up to 5.5. ARR for EDSS > 5.5 were based on the relative increases in ARR as reported in the Patzold study (Patzold et al., 1982).	CIS RRMS SPMS	Relative risks of relapse were estimated from RSS data. A distinction was made between moderate and severe relapse. ARR was applied to the proportion of relapses that were severe. For Copaxone this was 0.796 (source, COMI 2000 European Canadian). For other DMTs this ranged from 0.495 (PegINFβ-1a) to 1.282 (Tecfidera).
Adverse events	Annualised risks for adverse events were considered for all treatments. AEs for people in the BSC arm were not considered. Annualised risks for each treatment were qualitatively analysed. Adverse events reported from the ADVANCE study which were >5% for any DMT or >3% for all treatments were included in the economic analysis	5.1% experience adverse events every year on DMDs. Adverse events associated with utility decrement of 0.02	The nature and rate of adverse events were derived from pooled clinical trial data. The assumed probability of an adverse event on Copaxone was 0.481 (1st and 2nd year). For other DMTs, the probabilities ranged from 0.32 (Tecfidera) to 0.752 (pegIFNβ-1a). The disutility of an AE was 0.004 QALYs for Copaxone, and ranged from 0.000 (Gilenya, Tecfidera) to 0.004 QALYs (Copaxone, pegIFNβ-1a)
Mortality	Mortality was assumed to be equivalent between RRMS and SPMS, and dependent on the EDSS level	Utilised DH/RSS approach for base-case analysis. This involved applying a SMR of 2.0 to life table estimates and a MS specific	An EDSS-dependent mortality multiplier was used to estimate mortality from UK general population rates (sourced from ONS data for 2012-2014). These multipliers were taken from

		mortality rate for those with EDSS score 6 or higher.	the Teriflunomide manuf submission to NICE (which were adapted from Pokorski et al 1997)
Time horizon	50-year time horizon	50-year time horizon	50-year time horizon
Base-case analysis results	SC pegINFβ-1a 125µg compared to best supportive care had an ICER of approximately £31,000 per QALY	CIS ICER: [redacted] gained RRMS ICER: [redacted] gained SPMS ICER: [redacted] gained	Copaxone incremental cost-effectiveness ratio (ICER) of [redacted] per quality-adjusted life year (QALY) vs best supportive care [redacted] when excluding support for nursing/infrastructure costs) in the DoH agreed analysis. De novo model [redacted] per QALY for Copaxone vs best supportive care. Copaxone was [redacted]
Sensitivity analysis (and PSA) results	All base-case results except the hazard ratio for the confirmed disability progression were robust to sensitivity analysis. At a willingness-to-pay threshold for a QALY, SC pegINFβ-1a 125µg had a <0.4 probability of being cost-effective when compared to best supportive care	CIS ICER: [redacted] gained RRMS ICER: [redacted] gained SPMS ICER : [redacted] gained	[redacted] of cost-effectiveness at £20,000 vs best supportive care. The cost-effective results were most sensitive to the choice of data informing the hazard ratio for progression

ARR, annualised relapse rate; DoH, Department of Health; EDSS, expanded disability status scale; ICER, incremental cost-effectiveness ratio; MS, multiple sclerosis; NICE, National Institute for Health and Care Excellence; ONS, Office National Statistics; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-years; RRMS, relapsing-remitting multiple sclerosis; RSS, Risk Sharing Scheme; SC, subcutaneous; ScHARR, School of Health and Related Research; SPMS, secondary progressive multiple sclerosis

14.4 *Summary and critique of the companies' submissions*

14.4.1 Overview of company submissions

This section provides an overview of the economic evidence submitted by the three companies: (1) Biogen Idec ltd; (2) Teva UK Limited; and (3) Merck Biopharma. We provide a summary of the company submissions and an assessment of how they compare to the NICE reference case, and of how they differ to each other and to the DH RSS model analysis.

Biogen Idec ltd undertook an economic analysis to assess the costs-effectiveness of their disease modifying treatments, IFN β-1a 30 µg IM once weekly (Avonex) and pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy), and other DMTs on the market, including IFN β-1a 44 or 22 µg SC three times weekly (Rebif), IFN β-1b 250 µg SC every other day (Betaferon/Extavia), and GA 20 mg SC daily or 40 mg SC three times weekly (Copaxone). Teva UK Ltd. undertook a comparable economic analysis of their DMT, GA 20 mg SC daily or 40 mg SC three times weekly (Copaxone), and others on the market, including IFN β-1a 30 µg IM once weekly (Avonex), pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy), IFN β-1a 44 or 22 µg SC three times weekly (Rebif), IFN β-1b 250 µg SC every other day (Betaferon/Extavia), fingolimod (Gilenya), natalizumab (Tysabri), and dimethyl fumarate (Tecfidera), whilst Merck Biopharma undertook an economic analysis of only their disease modifying treatment, IFN β-1a 44 or 22 µg SC three times weekly (Rebif).

In the primary analysis, all three companies undertook an economic analysis of DMTs compared with best supportive care for people with relapsing-remitting multiple sclerosis (RRMS). The three companies clearly state their decision problem, which is consistent with NICE's scope for the appraisal.

14.4.2 Type of multiple sclerosis

Biogen and Teva only undertook a cost-effectiveness analysis of DMTs for those with RRMS. Merck also evaluated the cost-effectiveness of their DMT in patients presenting with SPMS and with CIS.

14.4.3 Analysis (cycle length, time horizon, perspective)

All three companies followed the same approach with regards to the model analysis, perspectives, outcome measures and time horizon for analysis. They all undertook a cost utility analysis from the National Health Service (NHS) and Personal Social Services (PSS) perspective. The outcome measure used in the analysis was quality-adjusted life-years gained, over a 50-year time horizon with annual cycle lengths. Results were presented as an ICER and expressed as cost per QALYs gained. Both costs and benefits were discounted at 3.5% per annum.

The perspectives used in the three company submissions, in terms of costs and health outcomes, are in accordance to the NICE reference case. All three companies undertook cost-utility analysis and measured health outcomes in QALYs, and present the ICER estimates, as advocated in the NICE reference case. In their base-case analysis all three companies evaluated the decision over a 50-year time horizon, with the starting age for the population modelled aged >=30 years. The time horizon on the analysis should be sufficiently long to reflect differences in costs and outcomes.

14.4.4 Model structure

All three company submissions utilised a Markov cohort model, based on the original ScHARR model[257] to undertake their cost-effectiveness analysis. Broadly all the company submissions used EDSS scores to define RRMS and SPMS health states, with 10 mutually exclusive EDSS defined health states. In all the models, people with RRMS could progress, regress (improve) or stay in the same EDSS health state, or progress from RRMS to SPMS. People could not move from SPMS to RRMS, and once progressed to SPMS, individuals' EDSS scores could not improve.

There were some differences between the company submissions regarding when DMTs were stopped in the model analysis. In the Biogen company submission, DMTs were assumed to be stopped once patients progressed to SPMS. Teva discontinued DMTs once EDSS score ≥7, or when patients had progressed to SPMS. Merck discontinued DMTs once EDSS score ≥7, irrespective of whether patients had progressed to SPMS. In all three company submissions, DMTs were stopped if patients experienced adverse drug reactions. When DMTs are stopped is likely to impact on the modelled lifetime costs, and therefore the ICER estimate.

14.4.5 Interventions evaluated

All three company submissions compared the treatment of RRMS with DMTs to providing best supportive care. For SPMS Merck compared IFN β-1a 44 or 22 µg SC three times weekly (Rebif) to best supportive care, and for CIS they also compared IFN β-1a 44 or 22 µg SC three times weekly (Rebif) to best supportive care with DMTs started once progressed to RRMS.

14.4.6 Population modelled

There were differences between the three company submissions in how they determined the population to be modelled. Teva and Merck used the population characteristics (age; sex distribution; starting EDSS scores) observed in the RSS cohort data, whilst Biogen used the baseline characteristics observed in the ADVANCE trial.[211] Major differences include the mean age of onset of RRMS. In the Biogen model this was 36 years, whilst in the Teva and Merck models, this was 30 years. Also in the Biogen model approximately 32% of the cohort modelled started with a EDSS score <=1, whilst in the Teva and Merck models between 19% and 23% of the cohort modelled started with a EDSS score <=1. The age of the population is likely to impact on modelled lifetime costs and lifetime quality adjusted years. For example, modelling cost-effectiveness of DMTs in an older population will likely result in lower total lifetime costs and lower total lifetime quality adjusted years, but how this impacts on the ICER estimate may be complex. In addition, the initial distribution of EDSS scores in the population modelled will also have an impact on lifetime costs and quality-adjusted years, especially as higher EDSS health states are associated with higher costs and poorer utility weights than lower EDSS health states. Again how this impacts on the ICER is complex. The assessment group cosnider that the age, sex and EDSS scores amongst those in the RSS dataset better reflect the UK RRMS population than participants recruited into a clinical trial.

14.4.7 Transition probabilities: disease progression, relapse and mortality

The company submissions used different approaches to model disease progression for those on best supportive care (BSC). Biogen derived transition probabilities using disability progression observed amongst the placebo arm of the ADVANCE trial[211] supplemented with information from the British Columbia dataset.[151] Teva used the London Ontario data[84] to derive the majority of their transition probabilities to model progression, whilst Merck used the British Columbia dataset. The data sources used to model disease progression for the BSC strategy is likely to impact on the ICER. Whilst it may be difficult to argue which of the London Ontario or British Columbia data sets provide the optimal representation of disease progression in MS patients not receiving DMTs, it would seem unorthodox to use patients recruited into the placebo arm of a clinical trial to represent this.

For relapse rates (annualised relapse rate) there were some differences in the data used by each company. All three company submissions applied EDSS health state specific relapse rates. Biogen estimated relapse rates using data obtained from the ADVANCE trial up to EDSS 5.5, and supplemented with rates derived from the Patzold et al. (2008) and the ADVANCE trial. Teva and Merck both followed the DH RSS model approach, and used the same relapse rates as in the previous ScHARR model.[257] The relapse rates (for BSC) used by Biogen tended to be lower, translating into fewer episodes and lower modelled lifetime costs and lifetime quality-adjusted years for those on BSC. How this impacts on the ICER estimate will also depend on the relapse rates assigned for the DMT strategy.

All three company submissions followed comparable approaches to modelling mortality. As with the RSS model, background all-cause mortality was derived from age and gender-specific mortality rates. In addition, an MS-specific mortality rate was included through mortality multipliers assigned to each EDSS health state.

Transition probabilities: treatment effect

All three company submissions followed comparable approaches to modelling the treatment effect of DMTs, however, there were some differences in the data sources used. Treatment effects included the impact of DMTs on disease progression and on relapses. A hazard ratio was applied to the natural history progression matrices to determine disease progression for those on DMTs. Biogen and Teva state they undertook a network meta-analysis to estimate the hazard ratios for disability progression. Of note, implied hazard ratios for pegylated IFN β-1a 125 µg SC every 2 weeks (Plegridy) are not available from the year-10 RSS dataset. However Merck state that they used the implied hazard ratio for disability progression from the 10-year RSS data provided by DH. Of note, the implied hazard ratios from the RSS datasets tended to be higher than those obtained from the network meta-analysis. A higher hazard ratio for disability progression will result in higher ICER estimates.

For relapse rates on DMTs, Biogen and Teva undertook a network meta-analysis whilst Merck extracted the value from the previous ScHARR model. As previously mentioned the Biogen used a different data source for relapse rates for BSC than the other two companies, with the relapse rates they used for BSC being lower. The relapse rates on DMTs obtained from the network meta-analysis tended to be lower that that obtained from the 10-year RSS datasets. Untangling the impact on the final ICER is complex, especially in the case of Biogen's

company submission. However, a greater effect of DMTs on reducing relapse rates will lead to smaller ICER estimates.

There were minor differences in how treatment discontinuation was modelled in the three company submissions. Biogen reported that they used the discontinuation rates observed in clinical trials of the DMTs. Teva and Merck followed the DH RSS model and assumed 5% would discontinue treatment per annum. The discontinuation rates used by Biogen were generally higher than 5% per annum for the DMTs they evaluated. A higher discontinuation rate will lead to lower lifetime costs but also lower quality adjusted years on DMTs. This may potentially impact on the ICER estimate.

There were significant differences in how treatment waning effect was modelled in the three company submissions. Biogen assumed that there would be no treatment waning effect in their base case analysis, and assumed that the efficacy of DMTs would be maintained. Teva and Merck followed the approach taken in the RSS model and assumed that after 10 years on DMTs, efficacy would be lower. Not including a waning effect will not impact on lifetime costs on DMTs but will increase quality-adjusted years on DMTs, and likely result in lower ICER estimates.

Although the NICE reference case highlights that systematic reviews should be undertaken to obtain evidence on outcomes, the RSS cohort long-term outcome data may be a more valid data source.

14.4.8 Resource use and costs

In all three company submissions, costs included in the analysis were those directly related to the NHS and PSS perspectives, with costs inflated to 2015 UK Sterling. There were some differences in the costs included by the three company submissions. All three companies included:

- Drug acquisition costs
- Administration costs
- Monitoring costs
- Health state/EDSS costs
- Cost of relapse
- Treatment-related adverse event costs

There were some differences in how the cost of providing DMTs (acquisition, administration and monitoring) was estimated and/or described. Biogen and Teva provide a detailed breakdown of the costs included, broken down by the cost for drug acquisition, administration and monitoring. Merck provided a single total cost for treatment with DMTs. It is unclear whether this estimate includes the cost of administering and/or monitoring treatment on DMTs. Additionally, the estimate used in the model analysis was classified as commercial in confidence material, and may not represent the list price for the drug. The total cost involved in providing DMTs to patients will be an important driver of cost-effectiveness. It does not seem that any of the three companies included the infrastructure costs (e.g nursing infrastructure) in the drug treatment costs.

Teva and Merck used previously reported resource use data in the ScHARR model to determine the costs to assign to EDSS defined health states. The costs assigned by Teva and Merck, adjusted to 2015 UK Sterling,

were approximately the same. Biogen reported that they used cost data reported in the UK MS Survey, and assigned different costs depending on both EDSS state and whether patients had RRMS or SPMS. The costs assigned to the EDSS states in Biogen's company submission tended to be lower than that used by Teva and Merck. This is likely to result in lower lifetime costs, but will affect both DMT and BSC strategies.

For the cost of relapse, the three companies followed the same approach. A proportion of those experiencing relapses would experience mild relapses (not requiring hospitalisation) whilst others would experience severe relapses (requiring hospitalisation). The costs of each type of relapse differed, so an average cost of relapse is estimated (based on proportions). The sources of the data differed, with Biogen using data from a recent study[111] whilst Teva and Merck inflated costs reported in the ScHARR model. The cost estimates used in Biogen's model were lower than those used in the Teva and Merck models.

Merck did not include the cost of treatment-related adverse events in the primary analysis, but included them their sensitivity analysis. Biogen and Teva included the costs of adverse events. Biogen undertook their own study with specialists (a Delphi panel) to estimate resource use for adverse events and consequently the unit costs. Teva derived the unit costs for adverse events using a combination of information from the PSSRU, national reference costs and the manufacturer submission for TA312.[269]

14.4.9 Health state utility values

There were some differences in the company submissions in the source of health state utility weights, and how they were assigned to the health states. In the company submissions by Teva and Merck, health state utilities for EDSS health states were derived by pooling data from the MS Trust and the Heron datasets (Orme et al., 2007). [105] Both assumed that the current EDSS score determined the utility scores for both the RRMS and SPMS health states. This was the approach used in the RSS model. Biogen derived utility weights differently in their model analysis. They used a combination of utility data from the ADVANCE study[211] and the UK MS survey, and their approach to pooling the data was driven by the data availability and not by standard methodological approaches to pooling data. In addition, Biogen assigned different utility weights for the EDSS health states by whether or not a patient had RRMS or SPMS. As the EDSS provides an assessment of disability, it may not be appropriate to apply a lower utility weight for the same EDSS score if patients had SPMS.

All three company submissions used different approaches to quantify the disutility from relapses. Teva and Merck assigned a disutility weight for a relapse and assumed the disutility from a relapse would last for duration between 46 to 90 days, with Teva further stratifying relapse disutility by the severity of the relapse (mild v severe). Although it is not clear, it seems that Biogen assumed the disutility from a relapse would persist and assigned an additional disutility to all EDSS health states (by subtracting the EDSS assigned utility by the relapse disutility) for those who had a relapse.

The above two issues highlight major differences in the utility weights assigned to the EDSS health states by Biogen, as compared to those assigned by Teva and Merck. The way in which this impacts on the ICER estimate is multifactorial and complex. There is a potential that this may lead to more favourable ICERs (greater QALY gain from DMTs) as one of the benefits of DMTs is to reduce relapses, and delay progression to SPMS.

There were also some minor differences in the data sources for quantifying carer's disutility in the company submissions. Teva and Merck followed the approach used in the RSS model by using data reported by Acaster et al. (2013),[261] but Biogen used data from the Orme study.[105] Overall this translated to Biogen assigning predominantly lower disutility weights for lower EDSS health states, and higher disutility weights for the two highest EDSS health states.

There were some minor differences in how disutilitiesfrom adverse drug reactions were modelled. All three companies assigned an average disutility, as was done in the RSS model. The average disutility was based on the proportion experiencing adverse events and the disutility weight attached to adverse drug reactions. Overall the values were not too dissimilar and are unlikely to impact on ICER estimates.

14.4.10 Summary

The assessment group reviewed the three company submissions from Biogen, Teva and Merck. Overall the methodological approaches used by the three companies are in accordance with the NICE reference case (see Table 61). There were however significant differences in the modelling approach and data sources used by each of the three companies, and this is likely to explain differences in the estimated ICERs. Importantly, there were significant differences between the approaches used by the companies to the approach used in the DH RSS model analysis. Biogen's submission differed most from the DH RSS model analysis, whilst Merck's company submission differed least.

Table 61: Company analyses against the NICE reference case

Element of health technology assessment	Biogen Idec	Teva UK Ltd	Merck Biopharma	Reference case
Defining the decision problem	✓	✓	✓	The scope developed by NICE
Comparator(s)	✓	✓	✓	As listed in the scope developed by NICE
Perspective on outcomes	✓	✓	✓	All direct health effects, whether for patients or, when relevant, carers
Perspective on costs	✓	✓	✓	NHS and PSS
Type of economic evaluation	✓	✓	✓	Cost–utility analysis with fully incremental analysis
Time horizon	✓	✓	✓	Long enough to reflect all important differences in costs or outcomes between the technologies being compared
Synthesis of evidence on health effects	✓	✓	✓	Based on a systematic review
Measuring and valuing health effects	✓	✓	✓	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults

Source of data for measurement of health-related quality of life	✓	✓	✓	Reported directly by patients and/or carers
Source of preference data for valuation of changes in health-related quality of life	✓	✓	✓	Representative sample of the UK population
Equity considerations	✓	✓	✓	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit
Evidence on resource use and costs	✓	✓	✓	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS
Discounting	✓	✓	✓	The same annual rate for both costs and health effects (currently 3.5%)

14.5 *Impact on the results based on the assumptions made by companies*

In order to understand the consequences of company assumptions, we have calculated results using company submitted treatment effects and list prices, but otherwise using RSS assumptions.

In these analyses, we retained the majority of the assumptions made in the RSS model but have made the following changes:

1. We excluded carers' disutilities,
2. We used the hazard ratios on the disability progression submitted by each company, and
3. We used the list price of disease modifying treatments.

Using the RSS base run and the time-varying models, we estimated the cost-effectiveness of DMTs (IFN β-1a 30 µg IM weekly (Avonex), IFN β-1a 44 µg SC three times weekly (Rebif), and glatiramer acetate 20 mg (Copaxone)) included in the RSS and with company submissions compared to best supportive care for people with RRMS. We present results in terms of total mean costs and total mean QALYs, and incremental cost-effectiveness ratio based on the cost per QALY gained. We report results based on a pairwise comparison (each DMT compared with best supportive care) and based on an incremental analysis. In the incremental analysis the strategies are ranked in ascending order on mean costs. We eliminated strategies where one strategy was cheaper and more effective (dominance). If there was a linear combination of two other strategies that were more costly and less effective (extended dominance), these were eliminated. For the remaining strategies we derived an incremental cost per QALY gained.

1.1.1.3 Results in terms of QALYs gained

At a 50-year time horizon, the results from the base run model showed that the best supportive care arm had expected mean costs of approximately £344,900 with a corresponding 8.451 QALYs. IFN β-1a 30 µg IM once weekly (Avonex) had mean costs of approximately [redacted] and corresponding [redacted] mean QALYs. Mean costs for IFN β-1a 44 µg SC three times weekly (Rebif) and glatiramer acetate 20 mg (Copaxone) were

approximately [redacted], with corresponding mean QALYs of [redacted], respectively. Results from the incremental analysis (see Table 62) showed that [redacted]. Excluding strategies that were dominated resulted in the comparison between best supportive care and [redacted]. Our pairwise analysis (see Table 63) showed that ICERs for each drug compared to best supportive care were different between the company submission and our estimates from the RSS model.

Table 62: Results based on the RSS model with individual company submission hazard ratios (incremental analysis)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	344,900	-	8.451	-	-
Glatiramer acetate 20 mg SC daily (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 30 µg IM weekly (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44 µg SC three times weekly (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 63: Comparison between incremental costs and QALYs submitted by each company and those derived using the RSS model (pairwise analysis)

Disease modifying treatment, company	Company's incremental costs	Incremental costs based on RSS model	Company's incremental QALYs	Incremental QALYs based on RSS model	Company's ICERs (£)	ICER (£) based on RSS model
IFN β-1a 30 µg SC once weekly (Avonex) (Biogen)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44 µg SC three times weekly (Rebif) (Merck)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg SC once daily (Copaxone) (Teva UK limited)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14.5.1 Discussion and conclusion

In this analysis, we compared DMTs with best supportive care, and report the incremental costs and QALYs for each company and those derived from using the RSS model. Of note we had concerns about the total quality adjusted life years estimated in the companies' submissions. The RSS model and our own cost-effectiveness model analysis estimated that for best supportive care in the base case analysis the mean quality adjusted life years to be approximately 8.5 QALYs, whilst Teva's model estimated it to be approximately [redacted] QALYs and Merck to be approximately [redacted] QALYs. When we adapted the RSS model to use disability progression from Teva and Merck, the mean quality adjusted life years approximated to 8.5 QALYs. We looked at a range of parameters that may affect this estimation: natural history cohort, utility values, mortality rates and starting EDSS distributions. Teva used the London Ontario dataset in order to model disease progression and this may explain why their estimate might have been different. We could not explain this difference between the findings from the RSS model and Merck's submission. All other aforementioned parameters were comparable between the models.

15 HEALTH ECONOMIC ASSESSMENT (RRMS)

15.1 *Objectives and methods*

15.1.1 Objectives

In Chapter 13, the assessment group outlined some limitations of the RSS model. We undertook several sensitivity analyses to address these concerns and to use alternative information sources and assumptions. We present these additional analyses undertaken by the assessment group below.

To assess the impact of disease modifying treatments used to treat people who were diagnosed with relapsing remitting multiple sclerosis, we developed a decision-analytical modelling framework which uses longitudinal data from natural history cohorts to provide information on the progression of RRMS. The objective of the model is to estimate the cost-effectiveness of disease modifying treatments within their marketing authorisation for treating people diagnosed with RRMS. In the model, health outcomes were measured in quality adjusted life years (QALYs), and we present results in terms of incremental cost per QALY gained. In the UK, an incremental cost-effectiveness ratio (ICER) below £20,000- £30,000 per QALY is considered cost-effective by decision-makers[273].

15.1.2 Methods: Developing the model structure

To estimate the cost-effectiveness of disease modifying treatments for treating people with RRMS, we used, rebuilt and developed the model structure for the RSS scheme submitted by the Department of Health. Details of the RSS model are outlined elsewhere in this report (see Chapter 13). Briefly, the RSS model is a cohort based Markov model. The model cycled yearly, with a starting age of 30 years and estimated the mean costs and effects associated with treatment compared with no treatment (best supportive care) over a 50-year time horizon. The analysis was conducted from the NHS and Personal Social Services (PSS) perspective and the results reported in terms of an incremental cost-effectiveness ratio, expressed as cost per QALYs gained. Both costs and benefits were discounted at 3.5% per annum. Health states for people with RRMS or secondary progressive multiple sclerosis (SPMS) were characterised by EDSS levels ranging from 0-10. In the model, transition matrices are applied to show how people move through the model. People are able to progress to more severe EDSS levels, regress to less severe EDSS levels, or there is a probability of dying from MS-related or other causes.

15.1.3 Methods: Model assumptions and characteristics changed from the RSS model in our analyses

The assessment group has assessed the impact of the following changes to the RSS model, which we discuss further below:

1. Use of discontinuation rates obtained from our clinical effectiveness review
2. Use of alternative estimates of treatment effectiveness (annualised relapse rates and hazard ratios for disability progression) derived from our clinical effectiveness review
3. Changes to mortality assumptions

4. Use of list prices for disease modifying treatments
5. Exclusion of carers' disutilities
6. Impact of varying key model input parameters
7. Implementation of probabilistic sensitivity analysis

15.1.4 Methods: Changes made to the RSS model

Discontinuation rates

In the treatment arm of the economic model it was assumed that every year 5% of people discontinued treatment as a result of adverse events. However, it was unclear whether this assumption was based on empirical evidence. We undertook further analyses to derive a combined discontinuation rate based on all the drugs used in the RSS and a discontinuation rate based on each individual drug used in the RSS model. These proportions were derived from the RRMS studies included in our clinical review. Studies reported the instantaneous rate of people who discontinued treatment as a result of disease modifying treatments. We converted this rate to an annual probability using the equation (probability = 1 – exp (-rt)), where r is rate and t is time.

Table 64: Annual proportion of people discontinuing treatment following adverse events

Parameter	Reported in RSS model	Derived from assessment group clinical review	Reported by each company	Derived from assessment group clinical review
IFN β-1a 30 µg IM once a week (Avonex)	0.0500	0.0229	0.0790	0.0150
IFNβ-1a pegylated 125 µg SC every 2 weeks (Plegridy)			0.1040	0.0150[a]
IFN β-1a 44/22 µg SC three times per week (Rebif)			0.0500	0.0263
IFN β-1b 250 µg SC every other day (Betaferon)			Not submitted	0.0219
Glatiramer acetate 20 mg SC daily or 40 mg SC three times a week (Copaxone)			0.0500	0.0263

DMT; disease modifying treatment; IFN, interferon
[a]We assumed that the discontinuation was the same as IFN β-1a 30 µg once a week (Avonex)

Table 64 shows the annual discontinuation rates for each disease modifying treatment, as well as the annual discontinuation rate for all disease modifying treatment combined. Our combined annual probability of 2.29% is lower than the discontinuation rate assumed in the RSS model. Using this value in the model would lead to more people remaining on treatment. Discontinuation rates reported by each company, tended to be lower than those derived from our clinical review.

Treatment effectiveness: annualised relapse rates

In the RSS model the annualised relapse rate for those treated with disease modifying agents as compared to those not treated was 0.72. We undertook further analyses to derive the annualised relapse rate based on the studies identified in our clinical effectiveness review to see how this compares with the value reported in the

RSS model, and with those reported in the companies' submissions. From our meta-analysis we derived a combined annualised relapse rate of 0.6494 (95% CI [0.5572, 0.7567]). Our annualised relapse rate is lower than the annualised relapse rate presented in the RSS model. The combined treatment effect from our network meta-analysis of the published studies suggests that there is a discrepancy in the assessment of the effectiveness of disease modifying therapies depending on the data source used. RCT evidence appears to show that disease-modifying therapies are more effective than is suggested by the RSS (see Table 65). In addition, we compared the annualised relapse rates for each individual disease modifying treatment derived from our network meta-analysis with the annualised relapse rates reported by each company. These two annualised rates appear to be very similar.

Table 65: Annualised relapse rates by DMT

Parameter	Reported by RSS (95% CI)	Derived from assessment group clinical review (95% CI)	Reported by each company (95% CI)	Derived from assessment group clinical review (95% CI)
IFN β-1a 30 µg IM once a week (Avonex)	0.72 (not reported)	0.6494 (0.5572, 0.7567)	[redacted]	0.80 (0.72, 0.88)
IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy)			0.6420 (0.4070, 1.0380)	0.64 (0.50, 0.83)
IFN β-1a 44 µg three times per week (Rebif)			0.670 (0.57, 0.79)	0.68 (0.61, 0.76)
IFN β-1b 250 µg every other day (Betaferon)			Not submitted	0.69 (0.62, 0.76)
Glatiramer acetate 40 mg three times a week with at least 48 hours apart (Copaxone)			[redacted]	0.66 (0.54, 0.80)
Glatiramer acetate 20 mg SC daily (Copaxone)			[redacted]	0.66 (0.59, 0.72)

DMT; disease modifying treatment; IFN, interferon

Treatment effectiveness: time to disability progression

We used both pooled and DMT-specific estimates of disability progression relative to best supportive care from our network meta-analyses and compared them to other relevant inputs.

First, we estimated a combined treatment effect of disease modifying treatments by pooling relevant active vs. placebo trials for on-scheme DMTs. Results showed a reduced hazard of sustained confirmed disability progression for people treated with disease modifying treatment compared to best supportive care. The HR was 0.6955 (95% CI [0.5530, 0.8747]). In contrast, the RSS model reported a reduced risk of sustained disease progression of HR 0.7913 (0.7705, 0.8122).

Second, we compared the estimates on disease progression reported by each company with the estimates derived from our analysis. Again, our results demonstrate a discrepancy between the effect sizes generated by the different sources of data (the RSS, the pooled RCT evidence, the effects reported by the companies and the

DMT-specific effects estimated in our network meta-analyses). Table 66 shows the treatment effects on disability progression, with assessment group values for disability progression confirmed at 3 months. We additionally considered disability progression confirmed at 6 months (see Table 67).

Table 66: Treatment effects on disability progression

Parameter	Reported by RSS model	Derived from assessment group clinical review	Reported by each company	Derived from assessment group clinical review
IFN β-1a 30 µg IM once a week (Avonex)	0.7913 (0.7705, 0.8122)	0.6955 (0.5530, 0.8747)	[redacted]	0.7300 (0.5300, 1.0000)
IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy)			0.620 (0.2090, 1.8150)	0.6200 (0.4000, 0.9700)
IFN β-1a 44 µg three times per week (Rebif)			[redacted]	0.6300 (0.4600, 0.8600)
IFN β-1b 250 µg every other day (Betaferon)			Not submitted	0.7800 (0.5900, 1.0200)
Glatiramer acetate 40 mg SC three times a week (Copaxone)			[redacted]	Not derived
Glatiramer acetate 20 mg SC daily (Copaxone)				0.7600 (0.6000, 0.9700)

DMT; disease modifying treatment; IFN, interferon

Table 67: Time to disability progression confirmed at 6 months

Parameter	Derived from assessment group clinical review
IFN β-1a 30 µg IM once a week (Avonex)	0.68 (0.49, 0.94)
IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy)	0.46 (0.26, 0.81)
IFN β-1a 44 µg three times per week (Rebif)	0.47 (0.24, 0.93)
IFN β-1b 250 µg every other day (Betaferon)	0.34 (0.18, 0.63)
Glatiramer acetate 40 mg SC three times a week (Copaxone)	Not reported
Glatiramer acetate 20 mg SC daily (Copaxone)	0.82 (0.53, 1.26)

DMT; disease modifying treatment; IFN, interferon

Mortality

The assessment group previously highlighted concerns regarding overestimation of MS-related mortality. In the RSS model we noted that individuals were subject to MS-related mortality (modelled as twice the standardised mortlity rate from other causes), in addition to mortality from transition to EDSS 10 (MS-related death). We highlighted that this would theorectically lead to double-counting of MS-related deaths in the model, and that results would therefore show a reduction in life years and QALYs gained. Hence, we changed the risk of MS-related death to the same as that for the general population, since the risk of MS-related death is already captured in the transition matrices. An alternative approach that we did not explore in these analyses would have been to to consider using mortality multipliers for lower EDSS levels to capture the increased risk of mortality for those with MS compared to the general popualtion.

Resource use and costs

The costs of disease modifying treatments were obtained from the British National Formulary 2016.[24] The annual cost of £8502 for treatment with IFN β-1a (Avonex) was derived based on the recommended dosage of 30 µg once a week. The annual cost of £10,572 for treatment with IFN β-1a (Rebif) was derived based on a dosage of 44 µg three times per week. We derived annual costs of £7264 and £6681 (£6724) for treatment with IFN β-1b 250 µg every other day (Betaferon) and glatiramer acetate (Copaxone) 40 mg SC three times weekly or 20 mg SC daily, respectively. Table 68 presents the costs for each disease modifying treatment. Of note, we have not specifically taken into account that those on IFN β-1a (Rebif) 44µg three times per week may subsequently have their dosage reduced to 22µg three times per week.

Table 68: Costs of disease modifying treatments

Disease modifying treatment	Cost (£, 2015)	Reference
IFNβ-1a (30 µg once a week)	8502	British National Formulary 2015[24]
IFNβ-1a pegylated (125 mcg every 2 weeks)	8502	
IFNβ-1a (44 µg three times per week)	10,572	
IFNβ-1b (250 µg every other day)	7264	
Glatiramer acetate (20 mg three times a week with at least 48 hours apart	6704	
Glatiramer acetate (40 mg three times a week with at least 48 hours apart	6681	

Utility values, including carers' disutilities

The assessment group considered the utility values used in the RSS analyses to be appropriate. However, we identified through literature searching other sources of utility estimates. In sensitivity analyses, we explored the impact of using these other sources of utility values.

Disutilities associated with caring for people with multiple sclerosis were included in the RSS analyses. However, it appears that carers included in the analysis represent informal/unpaid carers. The NICE reference case suggests that the perspective should be all direct health effects, whether for patients or other people. Hence, the assessment group has excluded carers' disutilities from the main analysis. We present analyses with the carer disutilities in Appendix 9.

15.1.5 Methods: Base case cost effectiveness analysis

The Markov model was developed and programmed to choose the base case model inputs in order to assess the cost-effectiveness of disease modifying treatments for the management of people with RRMS. The model estimated the mean costs and health benefits associated with each DMT, and assumed that the starting age of the population was 30 years old. **We consider the RSS model base case with changes made to avoid double counting of mortality and removal of carer disutilities to be our base case.** The analysis was undertaken from an NHS and PSS perspective in a specialist MS care setting and outcomes were reported as ICERs, expressed in terms of cost per QALY gained. All costs and outcomes were discounted at 3.5% per annum.

15.1.6 Methods: Sensitivity analysis

Multiway sensitivity analyses were undertaken, and these are summarised below:

1. **SA 1 Pooled on-scheme DMTs from assessment group review.** In this analysis, we used inputs from our review of the evidence pooled across all on-scheme DMTs. We used the aggregated hazard ratio for disability progression confirmed at 3 months, the aggregated annualised relapse rate, and the aggregated discontinuation rate.
2. **SA 2 Individual drugs from AG review**
    a. **Individual drugs from AG review, progression confirmed at 3 months.** Using the hazard ratio for disability progression confirmed at 3 months derived from our clinical effectiveness review, with the rate ratio for annualised relapse rate derived from our clinical effectiveness review, as well as relevant discontinuation rates and list prices
    b. **Individual drugs from AG review, progression confirmed at 6 months.** Using the hazard ratio for disability progression confirmed at 6 months derived from our clinical effectiveness review, with the rate ratio on annualised relapse rate derived from our clinical effectiveness review, as well as relevant discontinuation rates and list prices
3. **SA 3 Hazard ratios from company submissions.** Using the hazard ratios (confirmed disease progression) reported by each company with the annualised relapse rates reported by each company, as well as relevant discontinuation rates and list prices
4. **SA 4 Time horizon changed.** Individual drugs from AG review, progression confirmed at 3 months and relapse rate from clinical effectiveness review, relevant discontinuation rates and list prices, with time horizon changed from 50 years to 20 years or 30 years.
5. **SA 5 Parameter uncertainty analysis for the base case and SA 1.** We varied the hazard ratio for disability progression, the rate ratio for annualised relapse rates, cost of disease modifying treatments, and the annual discontinuation rate by ±10% for the base case and SA 1.

15.1.7 Methods: Probabilistic sensitivity analysis

We undertook probabilistic sensitivity analyses on the base case and SA 1 models to determine the uncertainty of the key model input parameters.

In the probabilistic sensitivity analysis, we varied the following parameters: hazard ratio for disability progression, rate ratio for annualised relapse rate, utility values for each EDSS state, disutility associated with relapses, management costs by EDSS state and costs of relapses, and assigned a distribution, which reflected the amount and pattern of its variation.

Standard errors for the annualised relapse rate reported in the RSS model were not available. Thus, we used standard errors derived from the pooled analysis of on-scheme DMTs to represent this uncertainty.

Cost-effectiveness results were calculated by simultaneously selecting random values from each distribution. The process was repeated 1000 times in a Monte Carlo simulation of the model to give an indication of how

variation in the model parameters lead to variation in the ICERs for a given treatment combination (e.g. disease modifying treatment compared with best supportive care).

In Table 69 we present the point estimates and the appropriate distribution for the input parameters. This type of analysis allows all parameter uncertainties to be incorporated into the analysis. Sampling parameter values from probability distributions, rather than from a simple range defined by the upper and lower bounds, places greater weight on the likely combinations of parameter values, and simulation results quantify the impact of uncertainties on the model in terms of the confidence that can be placed in the analysis results.

In Table 70, we summarise sensitivity analyses 1 through 4 with respect to key model parameters.

Table 69: Input parameters for RRMS economic assessment

Variable	Base-case value	95% confidence intervals	Distribution	Reference(s)
Baseline distribution of people in RSS				
EDSS 0	135	-	Fixed	Base case values obtained from the RSS model
EDSS 1	689	-	Fixed	
EDSS 2	1088	-	Fixed	
EDSS 3	970	-	Fixed	
EDSS 4	652	-	Fixed	
EDSS 5	441	-	Fixed	
EDSS 6	242	-	Fixed	
EDSS 7	0	-	Fixed	
EDSS 8	0	-	Fixed	
EDSS 9	0	-	Fixed	
EDSS 10	0	-	Fixed	
RRMS: relapse frequency (% of RRMS patients)				
EDSS 0	0.8895 (1.000)	-	Fixed	Base case values obtained from the RSS model
EDSS 1	0.7885 (0.861)	-	Fixed	
EDSS 2	0.6478 (0.861)	-	Fixed	
EDSS 3	0.6155 (0.806)	-	Fixed	
EDSS 4	0.5532 (0.545)	-	Fixed	
EDSS 5	0.5249 (0.343)	-	Fixed	
EDSS 6	0.5146 (0.270)	-	Fixed	
EDSS 7	0.4482 (0.053)	-	Fixed	
EDSS 8	0.3665 (0.000)	-	Fixed	
EDSS 9	0.2964 (0.000)	-	Fixed	
EDSS 10	0.0000 (0.000)	-	Fixed	
SPMS: relapse frequency (% of SPMS patients)				
EDSS 0	0.0000 (0.000)	-	Fixed	Base case values obtained from the RSS model

Variable	Base-case value	95% confidence intervals	Distribution	Reference(s)
EDSS 1	0.0000 (0.139)	-	Fixed	
EDSS 2	0.6049 (0.139)	-	Fixed	
EDSS 3	0.5154 (0.194)	-	Fixed	
EDSS 4	0.4867 (0.455)	-	Fixed	
EDSS 5	0.4226 (0.657)	-	Fixed	
EDSS 6	0.3595 (0.730)	-	Fixed	
EDSS 7	0.3025 (0.947)	-	Fixed	
EDSS 8	0.2510 (1.000)	-	Fixed	
EDSS 9	0.2172 (1.000)	-	Fixed	
EDSS 10	0.0000 (1.000)	-	Fixed	
Hazard ratio				
Disability progression in RSS model	0.7913	0.7705, 0.8122	Lognormal	Derived from assessment group analysis
Disability progression in assessment group model	0.6955	0.5530, 0.8747	Lognormal	
Rate ratio				
Annualised relapse rate in the RSS model	0.7200	0.5262, 0.7623	Lognormal	Base case valued obtained from RSS model, and confidence intervals derived from assessment group analysis
Annualised relapse rate in assessment group model	0.6494	0.5572, 0.7567	Lognormal	Derived from assessment group analysis
Management costs by EDSS				
EDSS 0	£1164	Assumed to lognormally distributed with standard error of 10% of the mean value	Lognormal	Base case values obtained from the RSS model
EDSS 1	£1164		Lognormal	
EDSS 2	£1164		Lognormal	
EDSS 3	£2147		Lognormal	
EDSS 4	£2225		Lognormal	
EDSS 5	£7840		Lognormal	
EDSS 6	£8746		Lognormal	
EDSS 7	£26,688		Lognormal	
EDSS 8	£41,439		Lognormal	
EDSS 9	£52,679		Lognormal	
EDSS 10	0		Fixed	
Management of relapse				
Cost of relapse	£4263	Assumed to lognormally distributed	Lognormal	Base case values obtained from the RSS model

Variable	Base-case value	95% confidence intervals	Distribution	Reference(s)
		with standard error of 10% of the mean value		
Utility values				
EDSS 0	0.9248	-	Beta (5.30, 1.33)	Base case values obtained from the RSS model, and ScHARR model
EDSS 1	0.7614	-	Beta (5.30, 1.33)	
EDSS 2	0.6741	-	Beta (5.30, 1.33)	
EDSS 3	0.5643	-	Beta (10.99, 3.21)	
EDSS 4	0.5643	-	Beta (64.35, 19.31)	
EDSS 5	0.4906	-	Beta (33.54, 10.35)	
EDSS 6	0.4453	-	Beta (6.43, 2.37)	
EDSS 7	0.2686	-	Beta (2.24, 2.28)	
EDSS 8	0.0076	-	Beta (1.27, 5.55)	
EDSS 9	-0.2304	-	Beta (0.38, 2.18)	
Dead	0	-	Fixed	By definition
Other				
Mortality (age-specific death rates)	Life tables	-	Fixed	ONS 2014, as cited in the Biogen submission
Discount rate per annum (costs and QALYs)	3.5%	-	Fixed	

EDSS, expanded disability status scale; ONS, office of National Statistics; QALYs, quality adjusted life years gained; RRMS, relapsing remitting multiple sclerosis; RSS, risk sharing scheme; SPMS, secondary progressive multiple sclerosis

Table 70: Summary of parameters across sensitivity analyses

Parameter	Base case analysis	SA1: Pooled on-scheme DMTs from assessment group review	SA 2a: Individual drugs from AG review, progression confirmed at 3 months	SA2b: Individual drugs from AG review, progression confirmed at 6 months	SA 3: Hazard ratios from company submissions	SA 4: Time horizon changed
Cost of disease modifying treatment	£7300	£7300	IFN β-1a 30 µg IM once a week (Avonex): £8502 IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): £8502 IFN β-1a 44 µg SC three times per week (Rebif): £10,572 IFN β-1b 250 µg every other day (Betaferon/Extavia): £7264 Glatiramer acetate 20 mg SC daily (Copaxone): £6704	IFN β-1a 30 µg IM once a week (Avonex): £8502 IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): £8502 IFN β-1a 44 µg SC three times per week (Rebif): £10,572 IFN β-1b 250 µg every other day (Betaferon/Extavia): £7264 Glatiramer acetate 20 mg SC daily (Copaxone): £6704	IFN β-1a 30 µg IM once a week (Avonex): £8502 IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): £8502 IFN β-1a 44 µg SC three times per week (Rebif): £10,572 IFN β-1b 250 µg every other day (Betaferon/Extavia): £7264 Glatiramer acetate 20 mg SC daily (Copaxone): £6704	IFN β-1a 30 µg IM once a week (Avonex): £8502 IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): £8502 IFN β-1a 44 SC µg three times per week (Rebif): £10,572 IFN β-1b 250 µg every other day (Betaferon/Extavia): £7264 Glatiramer acetate 20 mg SC daily (Copaxone): £6704
Pooled on-scheme DMTs on disability progression	0.7913	0.6955 (0.5530, 0.8747)	Not applicable	Not applicable	Not applicable	Not applicable
Individual drug time to disability progression	Not applicable	Not applicable	IFN β-1a 30 µg IM once a week (Avonex): 0.73 (0.53, 1.00) IFN β-1a pegylated 125 µg SC every 2 weeks	IFN β-1a 30 µg IM once a week (Avonex): 0.68 (0.49, 0.94) IFN β-1a pegylated 125 µg SC every 2 weeks	IFN β-1a 30 µg IM once a week (Avonex): [redacted] IFN β-1a pegylated 125 µg SC every 2 weeks	IFN β-1a 30 µg IM once a week (Avonex): 0.73 (0.53, 1.00) IFN β-1a pegylated 125 µg SC every 2 weeks

Parameter	Base case analysis	SA1: Pooled on-scheme DMTs from assessment group review	SA 2a: Individual drugs from AG review, progression confirmed at 3 months	SA2b: Individual drugs from AG review, progression confirmed at 6 months	SA 3: Hazard ratios from company submissions	SA 4: Time horizon changed
			(Plegridy): 0.62 (0.40, 0.97) IFN β-1a 44 µg SC three times per week (Rebif): 0.63 (0.46, 0.86) IFN β-1b 250 µg every other day (Betaferon/Extavia): 0.78 (0.59, 1.0) Glatiramer acetate 20 mg SC daily (Copaxone): 0.76 (0.60, 0.97)	(Plegridy): 0.46 (0.26, 0.81) IFN β-1a 44 µg SC three times per week (Rebif): 0.47 (0.24, 0.93) IFN β-1b 250 µg every other day (Betaferon/Extavia): 0.34 (0.18, 0.63) Glatiramer acetate 20 mg SC daily (Copaxone): 0.82 (0.53, 1.26)	(Plegridy): 0.620 (0.21, 1.82) IFN β-1a 44 µg SC three times per week (Rebif): [redacted] IFN β-1b 250 µg every other day (Betaferon/Extavia): NS Glatiramer acetate 20 mg SC daily (Copaxone): [redacted]	(Plegridy): 0.62 (0.40, 0.97) IFN β-1a 44 µg SC three times per week (Rebif): 0.63 (0.46, 0.86) IFN β-1b 250 µg every other day (Betaferon/Extavia): 0.78 (0.59, 1.0) Glatiramer acetate 20 mg SC daily (Copaxone): 0.76 (0.60, 0.97)
Aggregated annualised relapse rate	0.72	0.6494 (0.5572, 0.7567)	Not applicable	Not applicable	Not applicable	Not applicable
Individual drug annualised relapse rate	Not applicable	Not applicable	IFN β-1a 30 µg IM once a week (Avonex): 0.80 (0.72,0.88) IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): 0.64 (0.50,0.83)	IFN β-1a 30 µg IM once a week (Avonex): 0.80 (0.72,0.88) IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): 0.64 (0.50,0.83)	IFN β-1a 30 µg IM once a week (Avonex): 0.7870 (0.5990, 0.9790) IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): 0.6420 (0.4070, 1.0380) IFN β-1a 44 µg three times per week (Rebif): [redacted]	IFN β-1a 30 µg IM once a week (Avonex): 0.80 (0.72,0.88) IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): 0.64 (0.50,0.83)

Parameter	Base case analysis	SA1: Pooled on-scheme DMTs from assessment group review	SA 2a: Individual drugs from AG review, progression confirmed at 3 months	SA2b: Individual drugs from AG review, progression confirmed at 6 months	SA 3: Hazard ratios from company submissions	SA 4: Time horizon changed
			IFN β-1a 44 µg three times per week (Rebif): 0.68 (0.61, 0.76) IFN β-1b 250 µg every other day (Betaferon/Extavia): 0.69 (0.62, 0.76) Glatiramer acetate 20 mg SC daily (Copaxone): 0.66 (0.59, 0.72)	IFN β-1a 44 µg three times per week (Rebif): 0.68 (0.61, 0.76) IFN β-1b 250 µg every other day (Betaferon/Extavia): 0.69 (0.62, 0.76) Glatiramer acetate 20 mg SC daily (Copaxone): 0.66 (0.59, 0.72)	IFN β-1b 250 µg every other day (Betaferon/Extavia): NR Glatiramer acetate 20 mg SC daily (Copaxone): [redacted]	IFN β-1a 44 µg three times per week (Rebif): 0.68 (0.61, 0.76) IFN β-1b 250 µg every other day (Betaferon/Extavia): 0.69 (0.62, 0.76) Glatiramer acetate 20 mg SC daily (Copaxone): 0.66 (0.59, 0.72)
Annual discontinuation of treatment rate	0.05	0.0229	IFN β-1a 30 µg IM once a week (Avonex): 0.0150 IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): 0.0150 IFN β-1a 44 µg SC three times per week (Rebif): 0.0263 IFN β-1b 250 µg every other day (Betaferon/Extavia): 0.0219 Glatiramer acetate 20 mg SC daily (Copaxone): 0.0263	IFN β-1a 30 µg IM once a week (Avonex): 0.0150 IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): 0.0150 IFN β-1a 44 µg SC three times per week (Rebif): 0.0263 IFN β-1b 250 µg every other day (Betaferon/Extavia): 0.0219 Glatiramer acetate 20 mg SC daily (Copaxone): 0.0263	IFN β-1a 30 µg IM once a week (Avonex): 0.0790 IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): 0.1040 IFN β-1a 44 µg SC three times per week (Rebif): 0.0500 IFN β-1b 250 µg every other day (Betaferon/Extavia): NS Glatiramer acetate 20 mg SC daily (Copaxone): 0.0500	IFN β-1a 30 µg IM once a week (Avonex): 0.0150 IFN β-1a pegylated 125 µg SC every 2 weeks (Plegridy): 0.0150 IFN β-1a 44 µg SC three times per week (Rebif): 0.0263 IFN β-1b 250 µg every other day (Betaferon/Extavia): 0.0219 Glatiramer acetate 20 mg SC daily (Copaxone): 0.0263
Time horizon	50 years	50 years	50 years	50 years	50 years	20 years, then at 30 years

Parameter	Base case analysis	SA1: Pooled on-scheme DMTs from assessment group review	SA 2a: Individual drugs from AG review, progression confirmed at 3 months	SA2b: Individual drugs from AG review, progression confirmed at 6 months	SA 3: Hazard ratios from company submissions	SA 4: Time horizon changed
AG, assessment group; DMTs, disease modifying treatments; IM, intramuscular; NS, not submitted; SA, sensitivity analysis; SC, subcutaneous						

15.2 *Results of cost-effectiveness analysis*

We present analyses below relating to the base run model. Further results relating to the time-varying model can be found in Appendix 9.

15.2.1 Cost-effectiveness analysis results: base case and sensitivity analyses

Base Case

In Table 71, we present the findings from our base case analysis, taking into account the concerns described in above. The results showed that at a 50-year time horizon the DMT strategy was more costly and more effective than best supportive care. The expected mean costs per person for the disease modifying treatment strategy were approximately £25,600 more costly than the best supportive care strategy and produced 0.943 more QALYs with an ICER of approximately £27,200 per QALY.

Table 71: Base case results based cost per QALY

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
Disease modifying treatments	387,800	25,600	9.607	0.943	27,200
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

SA 1: Pooled on-scheme DMTs from assessment group review

We used two key estimates of treatment effectiveness from our clinical effectiveness review: the aggregated hazard ratio for disability progression confirmed at 3 months and the aggregated annualised relapse rate.

In Table 72, the results are presented in terms of cost per QALY. The results show that disease modifying treatment strategy was more costly and more effective than best supportive care alone. The disease modifying treatment strategy was approximately £14,800 more costly than best supportive care and produced 1.822 more QALYs, which equated to an ICER of approximately £8100 per QALY. This indicates that for every additional QALY from DMTs there is an incremental cost of £8100.

Table 72: Cost per QALY, SA 1

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
Disease modifying treatments	376,900	14,800	10.486	1.822	8100
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

SA 2a Individual drugs from AG review, progression confirmed at 3 months (preferred analysis)

In this model, we used the hazard ratios (DMT vs. placebo) for disability progression confirmed at three months (Table 66) and annualised relapse rates (Table 65) derived from our clinical effectiveness review applied to the individual DMTs.

Table 73: Cost per QALY, SA 2a (assessment group estimates, progression confirmed at 3 months)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
IFN β-1a 125µg (Plegridy)	379,900	17,800	11.223	2.559	7000
Glatiramer acetate 20mg (Copaxone)	381,400	1500	10.012	-1.211	Dominated
IFN β-1b 250µg every other day (Betaferon)	393,400	13,500	9.934	-1.289	Dominated
INF β-1a 44µg SC (Rebif)	404,800	24,900	10.867	-0.356	Dominated
IFNβ-1a 30µg IM (Avonex)	406,400	26,500	10.348	-0.875	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

Results from this sensitivity analysis (see Table 73) show that best supportive care was the least expensive strategy and IFN β-1a 30µg IM once weekly (Avonex) the most expensive. In terms of QALYs, best supportive care is expected to result in the least QALYs (8.664) and IFN β-1a 125 µg SC every two weeks (Plegridy) expected to yield the most QALYs (11.223). IFN β-1a 125 µg (Plegridy) dominated all other disease modifying treatment strategies being less costly and more effective. When compared to best supportive care, IFN β-1a 125 µg (Plegridy) was approximately £17,800 more costly and was more effective by expected mean gains of 2.559 QALYs, with an ICER of £7000 per QALY.

SA 2b: Individual drugs from AG review, progression confirmed at 6 months

In this sensitivity analysis, we used hazard ratios for disability progression confirmed at 6 months derived from our clinical effectiveness review, findings showed that IFN β-1a 125 µg SC every two weeks (Plegridy) was the least costly and most effective treatment strategy, dominating other treatment strategies included in this analysis (see Table 74). We did not include IFN β-1b 250µg every other day (Betaferon) in this analysis as its value for progression confirmed at 6 months was a) extreme, b) derived from indirect evidence, and c) driven by one open-label trial using an imputed hazard ratio.

Table 74: Cost per QALY, SA 2b (assessment group estimates, disability progression confirmed at 6 months)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)

IFN β-1a 125 µg SC every two weeks (Plegridy)	347,000	-	12.583	-	-
Best supportive care	362,100	15,100	8.664	-3.919	Dominated
IFN β-1a 44 µg SC three times a week (Rebif)	377,600	30,600	12.041	-0.542	Dominated
Glatiramer acetate 20 mg SC daily (Copaxone)	391,800	44,800	9.650	-2.933	Dominated
IFN β-1a 30 µg IM once weekly (Avonex)	397,200	50,200	10.717	-1.866	Dominated
BSC, best supportive care; IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

SA 3: Hazard ratios from company submissions

When we used the estimates for treatment effectiveness (annualised relapse rate and disability progression) reported by each company, results from this sensitivity analysis showed that best supportive care was the least expensive strategy and IFN β-1a 44µg SC three times a week (Rebif) was the most expensive (see Table 75). In terms of QALYs, best supportive care is expected to result in the least QALYs (8.664) and IFN β-1a 125 µg SC every two weeks (Plegridy) expected to yield the most QALYs (9.931). Results also showed that IFN β-1a 125 µg (Plegridy) dominated all other disease modifying treatment strategies. When compared to best supportive care, IFN β-1a 125 µg (Plegridy) demonstrated an ICER of £3300 per QALY.

Table 75: Cost per QALY, SA 3 (company estimates of effectiveness)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
IFN β-1a 125 µg SC every two weeks (Plegridy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 40 mg SC three times weekly (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 30µg IM once weekly (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44µg SC three times a week (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

SA 4: Time horizon changed from 50 years to 20 and 30 years

Table 76 and Table 77 show the results based on a 20-year and 30-year time horizon, respectively. These results showed that the glatiramer acetate treatment strategy is extendedly dominated by IFN β-1a 125 µg (Plegridy) in both analyses. Additionally, IFN β-1a 125 µg (Plegridy) dominated both IFN β-1a 30 µg IM (Avonex) and IFN β-1a 44µg SC (Rebif) treatment strategies. Excluding all dominated strategies, IFN β-1a 125 µg (Plegridy) when compared to best supportive care had an ICER of approximately £21,200 and £10,600 per QALY for the 20-year and 30-year time horizon, respectively.

Table 76: Cost per QALY, SA 3 (time horizon changed to 20 years)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	196,900	-	6.644	-	-
Glatiramer acetate 20mg (Copaxone)	220,900	24,000	7.436	0.792	Extendedly dominated
IFNβ-1a 125µg (Plegridy)	225,800	28,900	8.007	1.363	21,200
IFNβ-1a 30µg IM (Avonex)	242,900	17,100	7.570	-0.437	Dominated
INFβ-1a 44µg SC (Rebif)	245,200	19,400	7.882	-0.125	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous					

Table 77: Cost per QALY, SA 3 (time horizon changed to 30 years)

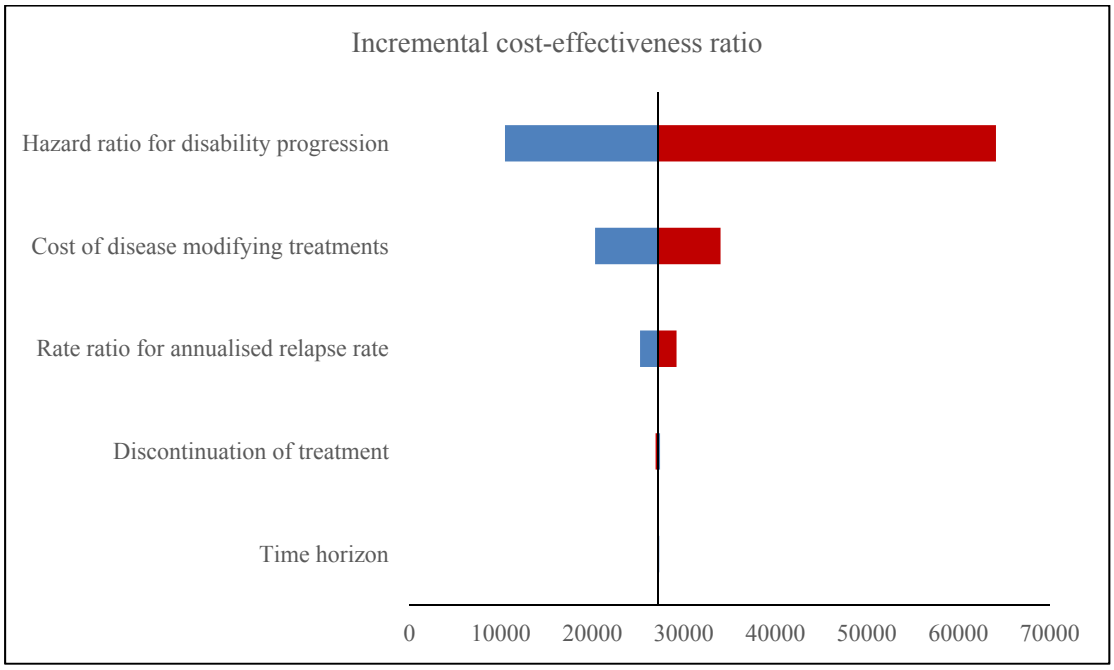
Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	279,400	-	7.774	-	-
Glatiramer acetate 20mg (Copaxone)	299,400	20,000	8.874	1.1	Extendedly dominated
IFNβ-1a 125µg (Plegridy)	300,400	21000	9.756	1.982	10,600
INFβ-1a 44µg SC (Rebif)	322,900	22500	9.532	-0.224	Dominated
IFNβ-1a 30µg IM (Avonex)	323,300	22,900	9.103	-0.653	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous					

SA 5: Parameter uncertainty analysis

Figure 26 shows a graphical representation (also known as a tornado diagram) of the impact **on the base case** of varying key model input parameters. In this analysis, we varied the hazard ratio for disability progression, the rate ratio for annualised relapse rates, cost of disease modifying treatments, and the annual discontinuation rate

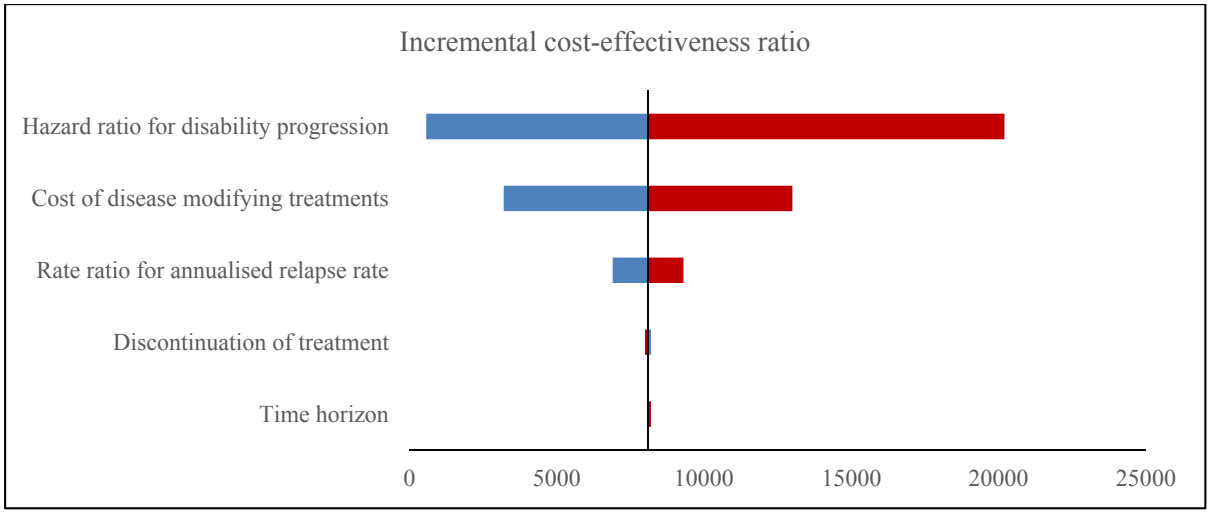
by ±10%. Additionally, we assessed the impact of the base case results by varying the model time horizon by ±10%. The results show that changes to the hazard ratio for disability progression have the greatest impact on the cost-effectiveness results. A decrease in the treatment effect (increase in the hazard ratio) by 10% resulted in an ICER of approximately £64,000 per QALY gained. An increase in the treatment effect (decrease in the hazard ratio) by 10% resulted in an ICER of approximately £10,400 per QALY gained. The model remained robust to changes to the treatment discontinuation rate and the model time horizon.

Figure 26: Base case tornado diagram for DMTs vs. best supportive care



In Figure 27, we show the impact **on the model estimated in SA 1** of varying model input parameters on the cost-effectiveness results. In SA 1, model input parameters were based on pooled estimates of treatment effectiveness for on-scheme DMTs. To determine the robustness of these results we varied the hazard ratio for disability progression, the rate ratio for annualised relapse rates, cost of disease modifying treatments, the annual discontinuation rate, and the model time horizon. The results show that the model was sensitive to changes to the cost of disease modifying treatment. An increase by 10% in cost of disease modifying treatment led to an increase in the incremental cost-effectiveness ratio by 60%. A decrease by 10% of the cost of DMTs led to a decrease in the ICER by approximately 61%. These results remained robust to changes made to annualised relapse rate, model time horizon and discontinuation of treatment.

Figure 27: SA 1 tornado diagram for DMTs vs. best supportive care



Probabilistic sensitivity analysis conducted on the base case

Table 78 presents the results of the probabilistic sensitivity analysis **conducted on the base case,** that is, when the RSS data were used to estimate the hazard ratio for disability progression and the rate ratio for annualised relapse rates. These results show that the disease modifying treatment strategy was more costly and more effective than best supportive care, with an ICER of approximately £32,000 per QALY gained.

Table 78: Findings from the probabilistic sensitivity analysis conducted on the base case

Strategy	Mean cost(£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	363,900	-	12.65	-	-
Disease modifying treatments	389,200	25,300	13.45	0.79	32,000
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Figure 28 shows the cost-effectiveness plane for the results from the 1000 simulations from the probabilistic sensitivity analysis conducted on the base case, and Figure 29 shows the proportion of these simulations at various willingness-to-pay thresholds in the form of a cost-effectiveness acceptability curve. The cost-effectiveness plane shows that a substantial number of simulations are in the north-east quadrant, where disease modifying treatments are more effective and more costly than best supportive care. We believe that the hazard ratio for disability progression is likely to be one of the key drivers of the economic model. The results from the cost-effectiveness acceptability curve show that at a willingness-to-pay threshold of £20,000 per QALY, disease-modifying treatment when compared to best supportive care, has a probability of being cost-effective of 0.37. It is important to note that the probabilistic sensitivity analysis shows a small but significant number of simulations where best supportive care dominates treatment with disease modifying drugs (north-west quadrant).

Figure 28: Cost-effectiveness plane, probabilistic sensitivity analysis conducted on the base case

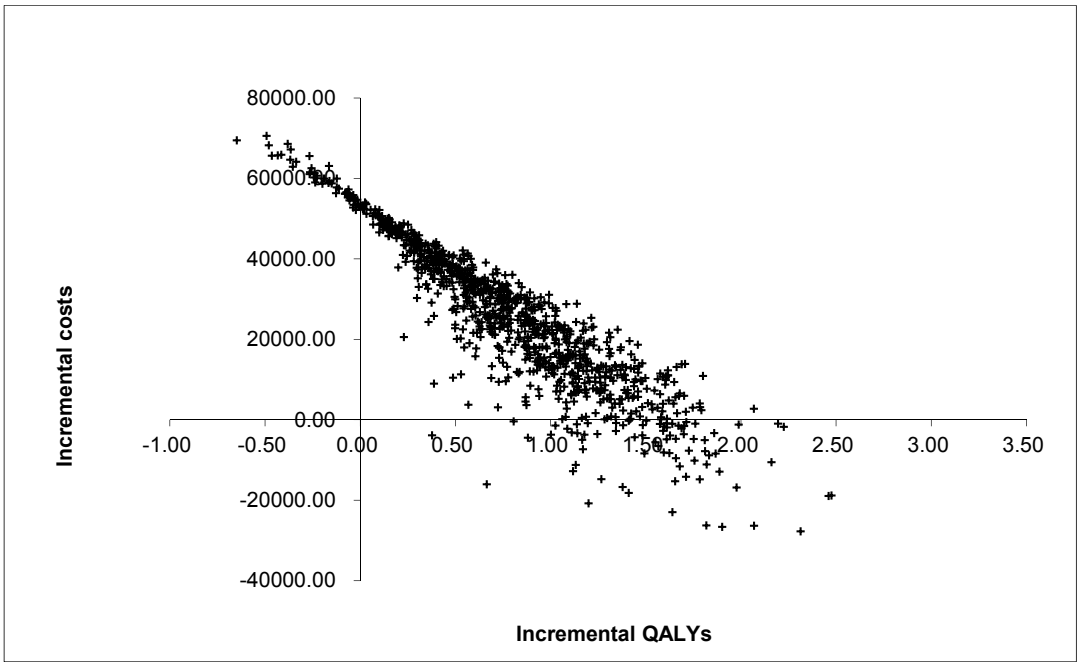
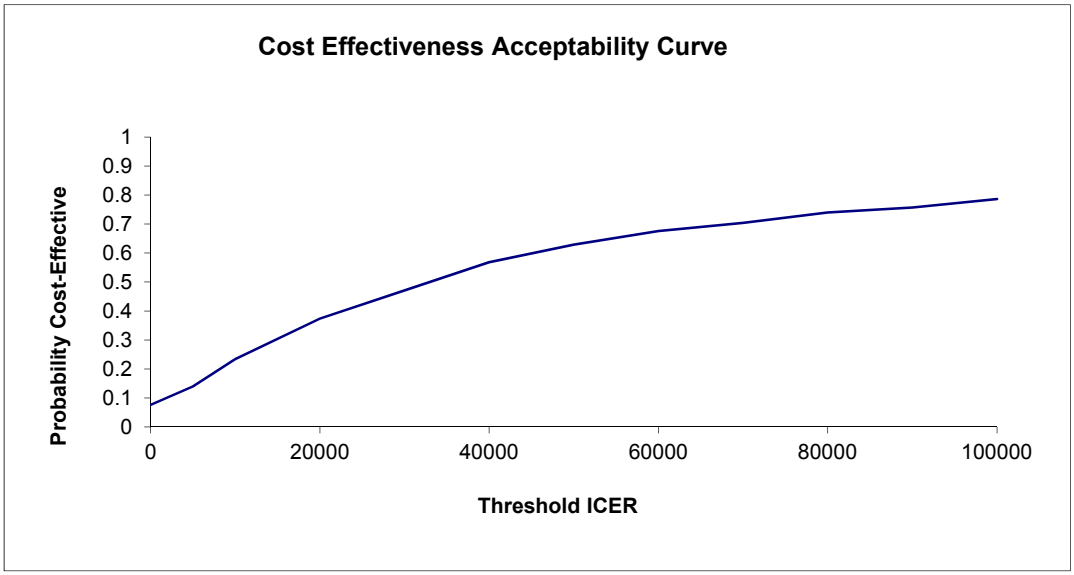


Figure 29: Cost-effectiveness acceptability curve, probabilistic senstivity analysis conducted on the base case



Probabilistic sensitivity analysis conducted on SA 1

Table 79 presents the results of the probabilistic sensitivity analysis when the findings from the assessment group review were used to estimate the pooled hazard ratio for disability progression and the pooled rate ratio for annualised relapse rates. The probabilistic sensitivity analysis shows that the ICER for disease modifying treatments compared to best supportive care was approximately £8000 per QALY gained.

Table 79: Findings from the probabilistic sensitivity analysis conducted on SA 1

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)

Best supportive care	364,400	-	12.70	-	-
Disease modifying treatments	374,100	9700	13.91	1.21	8000
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Results from the simulations are also presented on a cost-effectiveness plane (Figure 30), and cost-effectiveness acceptability curve (Figure 31). Results from 1000 simulations show that a substantial number of points are in the northeast quadrant. Importantly, a significant number of simulations from the PSA were in the southeast quadrant, where disease-modifying treatments could be considered more effective and less costly than best supportive care. The results from the cost-effectiveness acceptability curve show that at a willingness-to-pay threshold of £20,000 per QALY, and when compared to best supportive care, disease-modifying treatment has a probability of being cost-effective of 0.84.

Through visual inspection of the cost-effectiveness plane, it appears that the incremental costs of providing disease modifying treatments is correlated with the incremental effects from receiving treatment. We have undertaken further model simulations (not presented here). We kept the hazard ratio for disability progression constant, and varied other parameters. This resulted in the majority of the plots concentrated in the northeast quadrant and there was no correlation seen. This finding, in addition to the PSA findings presented in Figure 30 and Figure 31, highlight the fact that the hazard ratio for disability progression is likely to be one of the key drivers in the economic model. The more effective DMTs are in slowing disease progression, the more likely they are to be cost-effective.

Figure 30: Cost-effectiveness plane, probabilistic sensitivity analysis conducted on SA 1

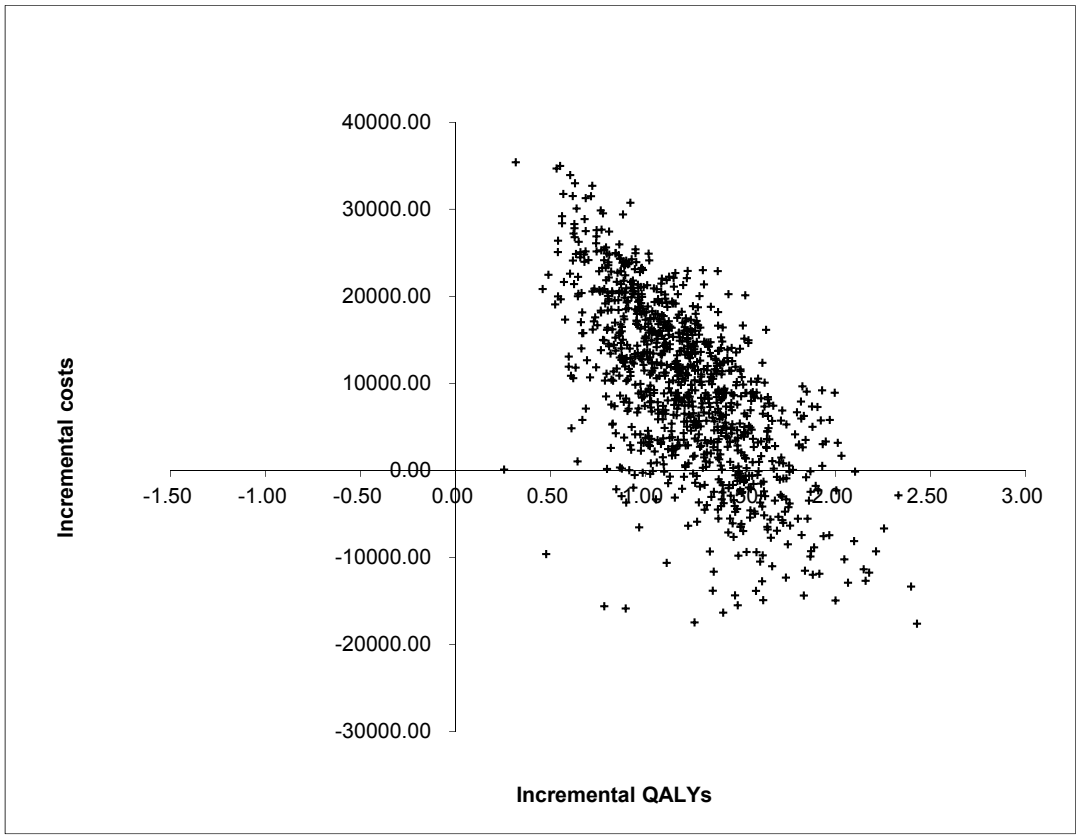
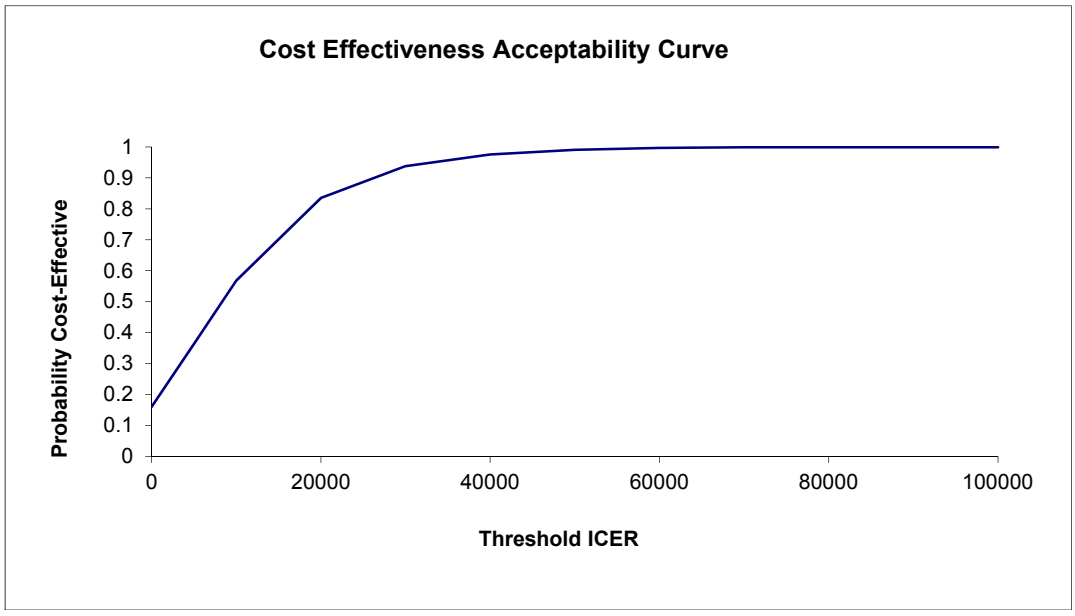


Figure 31: Cost-effectiveness acceptability curve, probabilistic sensitivity analysis conducted on SA 1



15.3 *Discussion of economic assessment of disease modifying treatments for relapsing remitting multiple sclerosis*

15.3.1 Summary of results

In this section, we estimated a variety of sensitivity analyses, in order to address our concerns with the RSS model. In the base case, we drew on the RSS model, and made a number of changes relating to mortality and carers' disutilities. Additionally, we undertook probabilistic sensitivity analyses for our estimates to incorporate uncertainty around input parameters. Deterministic results showed that disease-modifying treatment was more costly and more effective than best supportive care, with an ICER of approximately £27,200 per QALY gained. The PSA results, using the RSS data to estimate the parameters for treatment effectiveness, showed that disease modifying treatment when compared to best supportive care had a probability of 0.37 of being cost-effective at a willingness-to-pay threshold of £20,000 per QALY gained. Even at higher willingness-to-pay thresholds (e.g. £100,000 per QALY), the probability of disease modifying treatments being cost-effective does not reach 1, and some model simulations found best supportive care to dominate the provision of DMTs.

We undertook a number of further sensitivity analyses where we used hazard ratios for disability progression, and rate ratios for annualised relapse rate derived from our network meta-analyses. Deterministic results showed that disease-modifying treatment had an ICER of approximately £8100 per QALY gained when compared to best supportive care. Probabilistic results, using the assessment group data, showed that disease modifying treatment compared to best supportive care had a probability of 0.84 of being cost-effective at a willingness-to-pay threshold of £20,000 per QALY gained.

15.3.2 Strengths and limitations

There were several strengths to our analyses. First and foremost, we assessed the RSS model in detail, and we undertook a number of sensitivity analyses, including probabilistic sensitivity analyses, in order to explore our concerns with the RSS model. Second, we drew on rigorous evidence to estimate a comprehensive set of sensitivity analyses and used probabilistic sensitivity analyses to explore uncertainty. We were able to use clinical inputs from our own rigorous systematic review of the clinical effectiveness evidence, including our network meta-analyses for key treatment effectiveness parameters. This enabled us to compare the implications of different estimates of treatment effectiveness, including the RSS, the pooled on-scheme DMT effect sizes from our clinical effectiveness review, effect sizes for individual DMTs from the network meta-analyses contained in our clinical effectiveness review, and effectiveness estimates supplied by company submissions.

However, there were also limitations to our analyses. Where confidence intervals for input parameters were not provided for probabilistic sensitivity analyses, we had to apply commonly used approaches to model uncertainty. In particular, we did not have a confidence interval for the annualised relapse rate used in the RSS model, so we substituted the standard error from our meta-analysis. The effect of these strategies may be to incorrectly estimate the uncertainty around input parameters, and thus to over-estimate or under-estimate the probability estimate of DMTs being cost-effective at given willingness to pay thresholds. We were unable to include uncertainty around parameters for the natural history cohort used as a comparator in the RSS.

Moreover, any cost-effectiveness analyses undertaken using the estimates from our clinical effectiveness review propagate the major weaknesses identified with that evidence, including sparse networks of evidence, generally short-term follow-up, and differential risk of bias across comparisons. In particular, some estimates of intervention effectiveness, such as for IFN β-1a 125 µg SC every two weeks (Plegridy), relied on few studies; our assessment of Plegridy, in particular, relied on one trial with one year of follow-up connected to evidence networks only via placebo.

Finally, we chose as our base case the RSS model, which draws on observational evidence with a non-contemporaneous, historical control. However, we believed that the long-term follow-up, relevance to the NHS and to current clinical practice, and rigorous methods used in collecting and reporting data made it the best choice as a base case. In contrast, the evidence derived from the clinical effectiveness review had serious limitations discussed at the conclusion of Chapter 10. These limitations led us to believe, on balance, that the RSS was a better choice for the base case.

15.3.3 Conclusion of cost-effectiveness analysis

Based on the model and its inputs, the results of the base case, which draws on the evidence from the RSS, suggest that disease modifying treatment compared to best supportive care had a probability of 0.37 of being cost-effective at a willingness-to-pay threshold of £20,000 per QALY gained. Results from our pooled analysis of randomised controlled trials suggest a probability of 0.84 of disease modifying treatment being cost-effective at a willingness-to-pay threshold of £20,000 per QALY gained. The impact of disease modifying treatment on disability progression was found to be a key driver of cost-effectiveness. In the previous chapters, the clinical effectiveness review highlighted the differences in the estimates of effectiveness of disease modifying treatments, when derived from the RSS data and when derived from the network meta-analysis of clinical trials. The cost-effectiveness analysis in this section highlights how this difference in clinical effectiveness translates into apparent differences in conclusions on cost-effectiveness. However, any analyses undertaken on data from our review of clinical effectiveness propagate the weaknesses in that evidence, including short-term follow-up and sparse data for each comparison.

16 HEALTH ECONOMIC ASSESSMENT (CIS)

16.1 *Health economics methods*

16.1.1 Objective

Our objective was to undertake cost-effectiveness analysis to estimate the incremental cost per quality adjusted life year gained from providing DMTs to patients with clinically isolated syndrome (CIS). We developed a decision-analytical modelling framework, which uses longitudinal data from natural history cohorts and randomised controlled trials to provide information on the progression from CIS to RRMS. The modelling framework was informed by literature searches on model-based economic evaluations of interventions used to treat people with CIS, and longitudinal studies that tracked the progression/conversion of CIS to RRMS. The objective of the model is to estimate the cost-effectiveness of disease modifying treatments within their marketing authorisation for people with CIS. In the model, results are presented in terms of cost per QALY gained.

16.1.2 Developing the model structure

To assess the cost-effectiveness of DMTs for treating CIS, we developed a de novo economic model using TreeAge Pro 2013 software (TreeAge Software Inc., Williamstown, MA, USA).

The model represents, as far as possible, the clinical pathways that people would take while receiving treatment for CIS. Figure 32 shows an illustrative model structure. The model was structured in two stages: treatment of people with CIS and further progression to RRMS, and disease progression whilst in the RRMS health state. In the model we compared six strategies:

1. Best supportive care for people with CIS and RRMS
2. Best supportive care for people with CIS and disease modifying treatment for people converting to RRMS
3. Treatment with IFN β-1a 30 µg IM once weekly (Avonex) for people with CIS, continuing on DMTs after converting to RRMS
4. Treatment with IFN β-1b 250 µg SC every other day (Betaferon) for people with CIS, continuing on DMTs after converting to RRMS
5. Treatment with IFN β-1a 44 µg SC three times weekly (Rebif) for people with CIS, continuing on DMTs after converting to RRMS
6. Treatment with glatiramer acetate 20 mg once daily (Copaxone) for people with CIS, continuing on DMTs after converting to RRMS

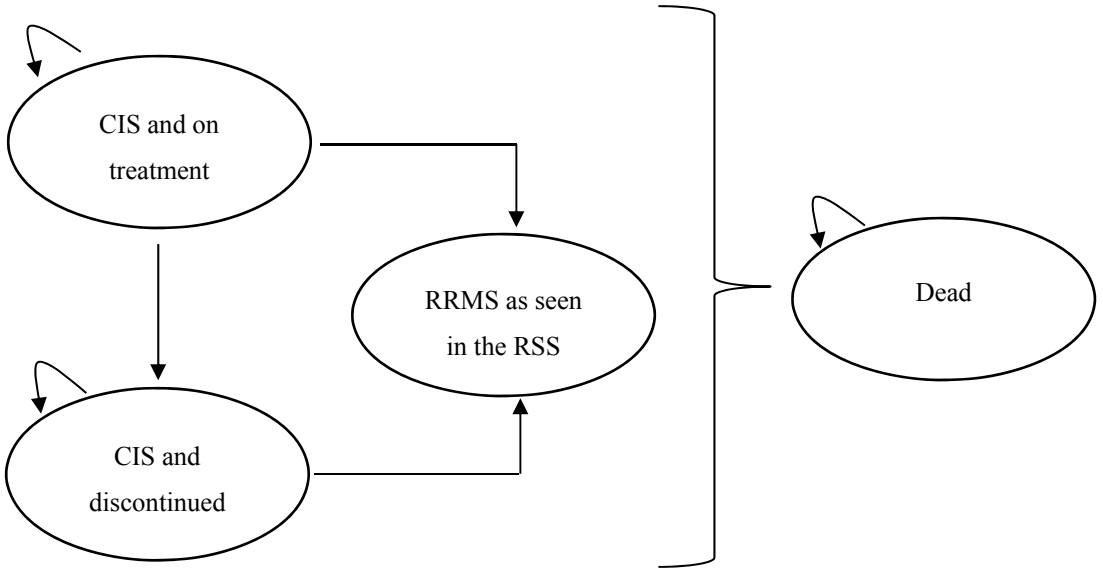


Figure 32: Illustrative model structure

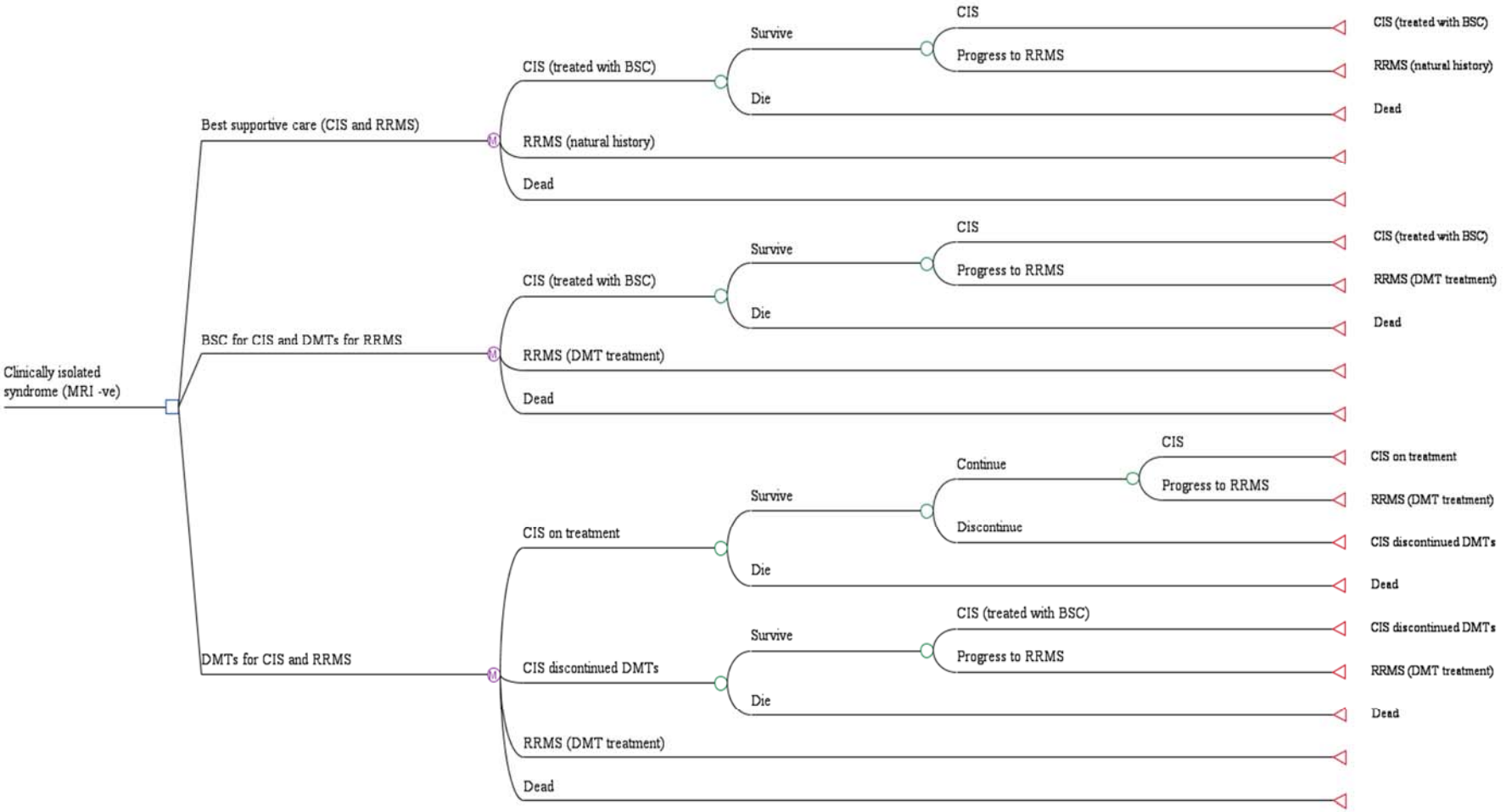


Figure 33: Pathway for the strategies being compared

16.1.3 Overview of strategies

An overview of how these strategies relate to the decision analytical model can be found in Figure 33.

Best supportive care arm for CIS and RRMS

In this strategy, people receive best supportive care as treatment for CIS. People who are alive can remain in this health state or progress to RRMS. People who progress to the RRMS health state are assumed to follow the pathway for people in the natural history cohort of the RSS model.

Best supportive care for CIS and DMTs for people with RRMS

In this strategy, people receive best supportive care as treatment for CIS. People who are alive can remain in this health state or progress to RRMS. People who progress to the RRMS health state are assumed to follow the pathway for people in the DMTs arm of the RSS model.

Disease modifying treatment for CIS and RRMS

People in this strategy receive a DMT for CIS. People can continue receiving treatment or discontinue treatment. People who continue treatment can remain in this health state or progress to the RRMS health state. People who convert to RRMS are assumed to follow the pathway for people in the DMTs arm of the RSS model. People who discontinue CIS treatment can remain in this health state whilst receiving best supportive care treatment or can convert to RRMS. We assumed that people who converted to RRMS follow the pathway for people in the DMTs arm of the RSS model. The pathway for people in the DMTs arm of the RSS model reflects the pooled estimates for all DMTs in the RSS model (e.g. drug acquisition costs), and consequently takes into account that whilst patients with CIS may discontinue the modelled DMT, when they progress to RRMS they may be started on an alternative DMT. The pathways for all DMTs for CIS being compared in the model are the same.

16.1.4 Model assumptions

A number of assumptions were required in order to undertake these analyses:

1. Starting population: People aged 30 years and with CIS, i.e. who had experienced a clinically diagnosed, single demyelinating event in one or several areas of the central nervous system within the last two months, and with no evidence of RRMS on MRI scan;
2. People who have converted to RRMS have no residual treatment benefit based on prior treatment in the CIS health state;
3. People who converted to RRMS are assumed to follow the same pathway as people in the RSS model; and

4. Patients with CIS who discontinue a DMT (e.g. due to adverse events) will be started on an alternative DMT once they progress to RRMS. The risk of patients with RRMS discontinuing a DMT is not dependent on whether or not they had discontinued a DMT whilst they had CIS.

16.1.5 Data required for the model

The model was populated with information identified from the clinical and cost-effectiveness review, and supplemented with information from secondary sources. Information required to parameterise the model included transition probabilities, resource use and costs, and utilities. These are discussed in turn below.

Transition probabilities and proportions

Information was required on the risk of disease progression from clinically isolated syndrome to relapsing remitting multiple sclerosis. Information on progression was required for an untreated cohort and for a treated cohort of people with CIS. For the untreated cohort, progression rates could be derived from a natural history cohort, patient registry or from CIS patients registered on a placebo arm of a trial. In the base case for the best supportive care arm, we identified one study[274] based on a literature review, which provided useful information on time to progression to RRMS for people diagnosed with clinically isolated syndrome with no asymptomatic lesions on magnetic resonance imaging (MRI). We reconstructed the Kaplan-Meier survival curve of time from first-attack to conversion to RRMS based on baseline MRI (no asymptomatic lesion) and fitted with various parametric models. According to the Akaike information criterion (AIC) and Bayesian information criterion (BIC), we found that the Weibull and loglogisitic models provided best fits to the Kerbrat et al.[274] data. Figure 34 shows the reconstructed Kaplan-Meier curve with the Weibull parametric model. From this, annual transition probabilities generated by the Weibull models were used for the best supportive care arm. To derive the transition probabilities on conversion to RRMS for the treatment arms, we applied the hazard ratios derived from our clinical review. Table 80 shows the estimates used to derive transition probabilities for conversion to RRMS in the model.

Figure 34: Reconstructed Kaplan-Meier and Weibull model for time to conversion to RRMS on best supportive care by annual cycles (Kerbrat et al., 2015)[274]

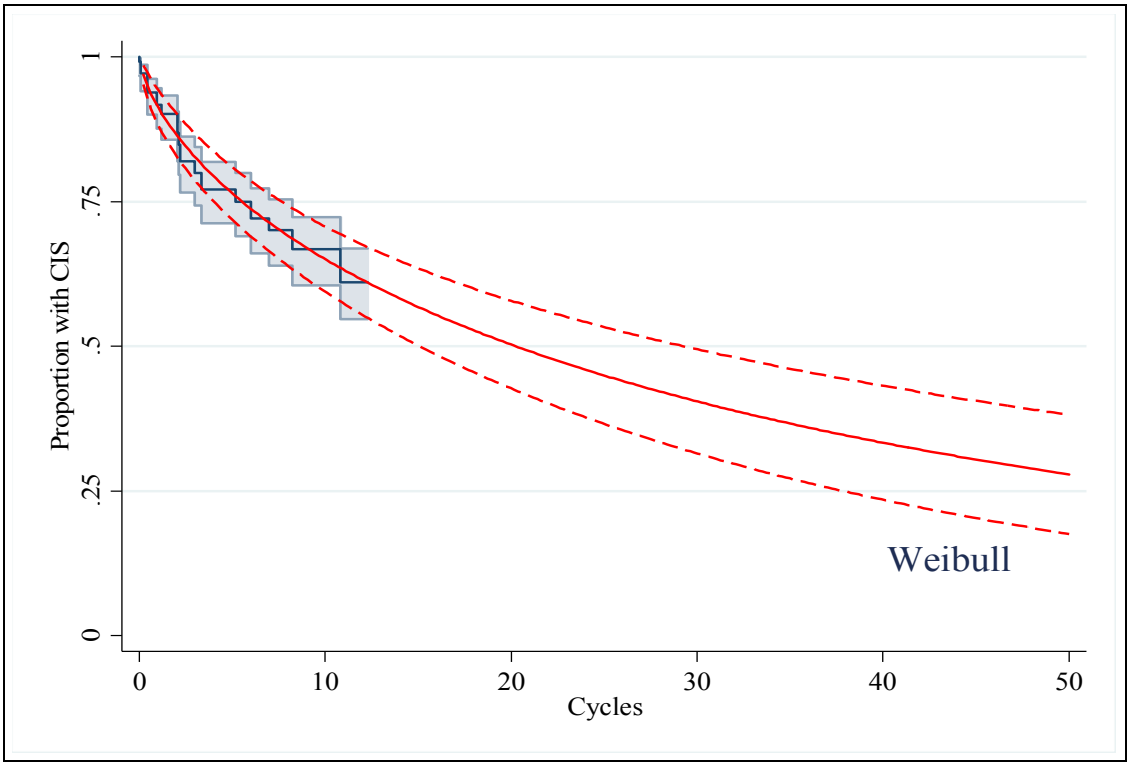


Table 80: Values for progression from CIS to RRMS

Parameter	Base-case value	Hazard ratios 95% CI	Reference(s)
Best supportive care	Weibull (λ = 0.0906; γ = 0.6768)	-	Kerbrat et al., 2015[274] (Reconstructed individual patient data and Weibull model was a good parametric fit); Applied hazard ratios derived from the clinical effectiveness review
IFN β-1a 30 µg IM once a week (Avonex)		0.516 (0.389, 0.684)	
IFN β-1a 44 µg SC three times per week (Rebif)		0.480 (0.314, 0.738)	
IFN β-1b 250 µg every other day (Betaferon)		0.500 (0.36, 0.699)	
Glatiramer acetate 20 mg SC daily (Copaxone)		0.549 (0.397, 0.762)	

Proportion of people discontinuing disease modifying treatment

We have included the annual proportion of people who discontinued DMT as a result of adverse events in the model. These proportions were derived from the CIS and RRMS studies included in our clinical review. Studies reported the instantaneous rate of people who discontinued treatment as a result of DMTs. We converted this to an annual probability using the equation (probability = 1 – exp (-rt), where r is rate and t is time. When discontinuation rates were not available from CIS studies, we used studies following up people with RRMS and assumed that the rates would be applicable to people with CIS. Table 81 shows the proportions obtained from the studies and the annual probability of discontinuation for each DMT used in the base case analysis.

Table 81: Proportion of people discontinuing treatment following adverse events

Parameter	Type of MS	Instantaneous rate	Annual probability	Reference
IFN β-1a 30 µg IM once a week (Avonex)	RRMS	4.4%	0.0222	Derived from Jacobs et al. (2000)[170]
IFN β-1a 44 µg SC three times per week (Rebif)	RRMS	6.0%	0.0330	Derived from Mikol et al. (2008)[190]
IFN β-1b 250 µg SC every other day (Betaferon/Extavia)	CIS	8.2%	0.0419	Derived from Kappos et al. (2006)[169]
Glatiramer acetate 20 mg SC daily (Copaxone)	CIS	5.8%	0.0197	Derived from Comi et al. (2009)

Resource use and costs

The resource use and costs utilised were those that were directly incurred by the National Health Service (NHS) and Personal and Social Services (PSS). Resource use and costs were required for DMTs, drug administration, monitoring costs and health state costs. Unit costs are presented in Table 82, and details on estimates of resource use are provided in Appendix 8.

Costs of disease modifying treatments were obtained from the British National Formulary 2015[24]. The annual cost of £8502 for treatment with IFN β-1a (Avonex) was based on a dosage of 30µg once a week. The annual cost of £10,572 for treatment with IFN β-1a (Rebif) was based on a dosage of 44µg three times per week. We derived annual costs of £7264 and £6704 for treatment with IFN β-1b 250 µg every other day (Betaferon/Extavia) and glatiramer acetate 20 mg SC daily (Copaxone), respectively.

Table 82: Unit costs required for the model

Parameter	Base-case value (£, 2015)	Reference(s)
IFN β-1a 30 µg IM once a week (Avonex)	8,502	British National Formulary (BNF), 2015[24]
IFN β-1a 44 µg SC three times per week (Rebif)	10,572	
IFN β-1b 250 µg SC every other day (Betaferon/Extavia)	7,264	
Glatiramer acetate 20 mg SC daily (Copaxone)	6,704	
Monitoring costs		
IFN β-1a 30 µg IM once a week (Avonex)	553.20	Estimates (see Appendix 8) on resource use from clinical expert and unit costs from BNF 2015[24], NHS reference costs 2014/15[275] and Curtis and Burns 2015[260]
IFN β-1a 44 µg SC three times per week (Rebif)	560.33	
IFN β-1b 250 µg SC every other day (Betaferon/Extavia)	553.20	
Glatiramer acetate 20 mg SC daily (Copaxone)	553.20	
Cost of subsequent monitoring	323.77	
Other costs		
Drug administration	225.00	Assumption on resource use information and unit costs from Curtis and Burns 2015[260]
Health state costs (CIS)		
CIS no treatment	350.49	Assumption on resource use information and unit costs from Curtis and Burns 2015[260] and NHS reference costs 2014/15[275]

CIS; clinically isolated syndrome; IFN, interferon

Costs for monitoring were derived based on clinical expert opinion for resource use and valued using costs from the NHS reference costs[275] and Curtis and Burns[260]. Monitoring costs were derived for initiating treatment, and costs for subsequent monitoring. We derived a cost of £553.20 for monitoring people who received treatment with IFN β-1a 30 µg IM once a week (Avonex), IFN β-1b 250 µg every other day (Betaferon/Extavia) and glatiramer acetate 20 mg SC daily (Copaxone) during the first year of commencing treatment. We assumed that people required visits to a neurologist and an MS nurse, and received a series of blood tests and an MRI scan. For people who commenced treatment with IFN β-1a 44 µg SC three times per week (Rebif), we derived a cost of £560.33. This included the same resources used, as described for the monitoring for other disease modifying treatments, in addition to a cost for a thyroid function test. For subsequent monitoring, we derived a cost of £323.77 for all disease modifying treatments. For this we assumed that people required visits to a neurologist and a MS nurse, and received an annual MRI scan. Further details of the resource use estimates are presented in Table 82.

We calculated an annual cost of administration of £225. For this we assumed a specialist nurse (community), employed on the NHS scale agenda for change Band 6 (£75 per hour of patient-related

work), would spend three hours of contact time to teach people how to self-administer disease modifying treatments.

Utility values

Health outcomes were measured in quality-adjusted life-years (QALYs). In the model, we assigned the same utility values to all the CIS health states. For this we have derived a weighted utility value based on two pooled utility values by EDSS health states (MS Trust survey 2002 and 2005) and weighted by the proportion of individuals at each EDSS health state observed on entry to the RSS cohort. The disutility associated with adverse events from DMTs was based on the estimates from Tappenden et al.[257] This was the approach used in the cost-effectiveness analysis of DMTs in RRMS. Table 83 shows the utility values used in the model.

Table 83: Utility values used in the CIS model

Parameter	Base-case value	Reference(s)
Health state utility values		
CIS	0.6218	Assumption
Disutility associated with AEs		Tappenden et al., 2001[257]
IFN β-1a 30 µg IM once a week (Avonex)	-0.02	
IFN β-1a 44 µg SC three times per week (Rebif)	-0.02	
IFN β-1b 250 µg SC every other day (Betaferon/Extavia)	-0.02	
Glatiramer acetate 20 mg SC daily (Copaxone)	-0.02	

AE, adverse events; CIS, clinically isolated syndrome

16.1.6 Cost-effectiveness analysis

A Markov model was constructed and programmed to choose the base case model inputs in order to assess the cost-effectiveness of various DMTs for the management of people with CIS. The model estimated the mean costs and health benefits associated with each DMT, and assumed that the starting population age of the population was 30 years old. The analysis was undertaken from a NHS and PSS perspective and outcomes were reported as ICERs, expressed in terms of cost per QALY gained. All costs and outcomes were discounted at 3.5% per annum.

16.1.7 Sensitivity analyses

A deterministic sensitivity analysis was undertaken for the base case results for the cost per QALY outcome measures, and these are summarised below:

1. SA 1 Changing the time horizon to 20 years and 30 years
2. SA 2 Assuming 5% of people with CIS would discontinue treatment with DMTs

In addition, we assessed the impact of varying key model input parameters on our base case results.

16.2 *Results of cost-effectiveness analysis*

16.2.1 Base case cost-effectiveness analysis

In Table 84, results for the base case analysis shows that providing best supportive care for people with CIS and continuing best supportive care on conversion to RRMS was the least costly strategy, with a mean cost of approximately £160,600, and the least effective, with a mean 12.78 QALYs gained. The strategy whereby people with CIS receive treatment with glatiramer acetate 20 mg SC daily (Copaxone), then receiving DMT when they convert to RRMS, dominated the IFN β-1a 30 µg IM once weekly (Avonex) and IFN β-1a 44 µg SC three times weekly (Rebif) treatment strategies. Excluding all dominated and extendedly dominated strategies, the optimal strategy was treatment with glatiramer acetate 20 mg SC daily (Copaxone). In comparison to best supportive care, providing glatiramer acetate 20 mg SC once daily (Copaxone) for patients with CIS, and DMTs on progression to RRMS, was associated with an ICER of £12,900 per QALY gained.

Table 84: Base case results, cost per QALY

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	136,800	-	12.78	-	-
BSC for CIS and DMTs for RRMS	150700	13900	13.16	0.38	Extendedly dominated
IFN β-1b 250 µg SC every other day (Betaferon/Extavia) for CIS and DMTs for RRMS	196,400	45,700	16.85	3.69	Extendedly dominated
Glatiramer acetate 20 mg SC daily (Copaxone) for CIS and DMTs for RRMS	213,700	76,900	18.73	5.95	12,900
IFN β-1a 30 µg IM once a week (Avonex) for CIS and DMTs for RRMS	231,300	17,900	18.57	-0.16	Dominated
IFN β-1a 44 µg SC three times per week (Rebif) for CIS and DMTs for RRMS	240,300	26,900	17.61	-1.12	Dominated

16.2.2 SA 1: Changing the time horizon to 20 years and 30 years

Table 85 and Table 86 show the findings when the model was run over time horizons of 20 years and 30 years. Over these shorter time horizons, treatment of CIS with IFN β-1b 250 µg SC every other day (Betaferon/Extavia) becomes cost-effective, with an ICER of £16,000/QALY gained and £13,500/QALY gained, for the 20-year and 30-year time horizons, respectively. Treatment with glatiramer acetate 20 mg SC daily (Copaxone) remains cost-effective. Over these shorter time horizons, treatment with IFN β-1a 30

µg IM weekly (Avonex) or IFN β-1a 44 µg SC (Rebif) continues to be dominated by glatiramer acetate 20 mg SC daily (Copaxone).

Table 85: SA 1 results (20-year time horizon)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	155,100	-	10.33	-	-
BSC for CIS and DMTs for RRMS	166,400	11,300	10.73	0.40	Extendedly dominated
IFN β-1b 250 µg SC every other day (Betaferon/Extavia) for CIS and DMTs for RRMS	181,600	26,500	11.99	1.66	16,000
Glatiramer acetate 20 mg SC daily (Copaxone) for CIS and DMTs for RRMS	190,400	8800	12.46	0.47	18,700
IFN β-1a 30µg IM weekly (Avonex) for CIS and DMTs for RRMS	204,100	13,900	12.39	-0.07	Dominated
IFN β-1a 44 µg SC three times weekly (Rebif) for CIS and DMTs for RRMS	215,000	24,800	12.15	-0.31	Dominated

Table 86: SA 1 results (30-year time horizon)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	173,100	-	12.02	-	-
BSC for CIS and DMTs for RRMS	185,600	12,500	12.46	0.44	Extendedly dominated
IFN β-1b 250 µg SC every other day (Betaferon/Extavia) for CIS and DMTs for RRMS	212,000	38,900	14.89	2.87	13,500
Glatiramer acetate 20 mg SC daily (Copaxone) for CIS and DMTs for RRMS	225,800	13,800	15.88	0.99	13,900
IFN β-1a 30µg IM weekly (Avonex) for CIS and DMTs for RRMS	241,200	15,700	15.78	-0.1	Dominated
IFN β-1a 44 µg SC three times weekly (Rebif) for CIS and DMTs for RRMS	251,000	25,500	15.28	-0.6	Dominated

16.2.3 SA 2 Assuming 5% of people with CIS would discontinue treatment with DMTs

Table 87 shows the findings when we assumed that approximately 5% of those treated with DMTs for CIS discontinue treatment every year. In this scenario, the treatment of CIS with IFN β-1b 250 µg SC every other day was cost-effective, with an ICER of £15,100/QALY gained. Treatment with glatiramer acetate 20

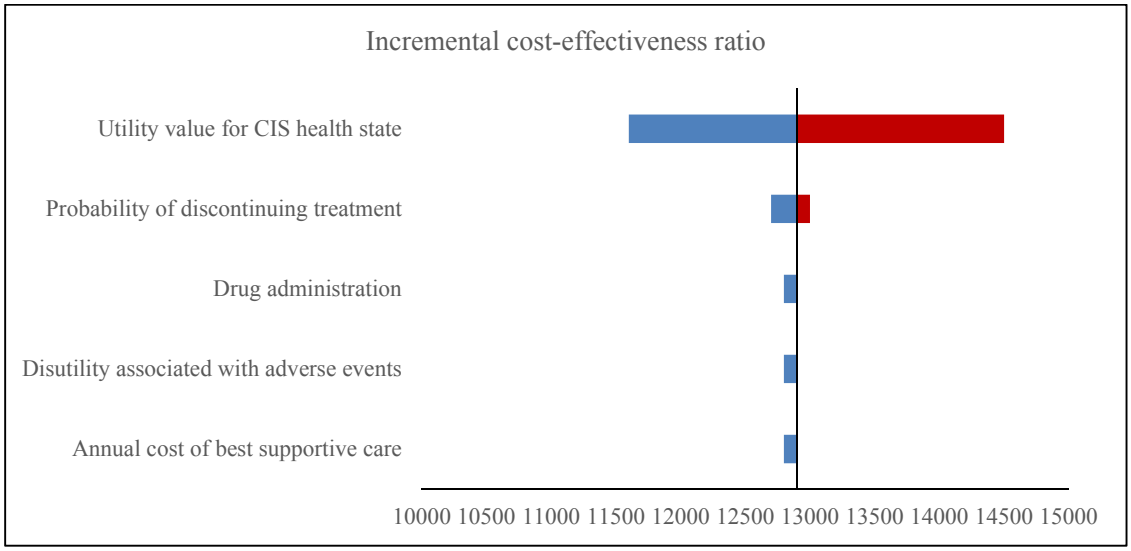
mg SC daily (Copaxone) remains cost-effective. However, treatment with IFN β-1a 30µg IM weekly (Avonex) or IFN β-1a 44 µg SC three times weekly (Rebif) continues to be dominated or associated with an extremely high ICER.

Table 87: SA 2 results (yearly discontinuation rate of 5%)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	136,800	-	12.78	-	
BSC for CIS and DMTs for RRMS	150,700	13,900	13.16	0.38	Extendedly dominated
IFN β-1b 250 µg SC every other day (Betaferon/Extavia) for CIS and DMTs for RRMS	188,700	51,900	16.22	3.44	15,100
Glatiramer acetate 20 mg SC daily (Copaxone) for CIS and DMTs for RRMS	191,100	2400	16.36	0.14	17,100
IFN β-1a 30µg IM weekly (Avonex) for CIS and DMTs for RRMS	204,000	12,900	16.31	-0.05	Dominated
IFN β-1a 44 µg SC three times weekly (Rebif) for CIS and DMTs for RRMS	222,200	31,100	16.41	0.05	622,000

In Figure 35, we present graphically the impact of varying model input parameters on the cost-effectiveness results. To determine the robustness of the results, we varied the utlity value for the CIS health state and the probability of treatment discontinuation as well as the mode of drug administration, the disutility associated with adverse events and the annual cost of BSC. The results show that the model was most sensitive to a +/- 10% change in the utility of the CIS health state. A 10% increase in the health state utility of CIS would take the value to 0.6898. However, this would still give an ICER for glatiramer acetate 20 mg (Copaxone) vs. BSC of £14,500, well within the normal expected levels of willingness to pay.

Figure 35: Tornado diagram for glatiramer acetate 20 mg SC daily vs. BSC



16.3 *Discussion of economic assessment of DMTs for CIS*

16.3.1 Summary of results

Having estimated the treatment effect of each DMT on the conversion to RMS, we then assessed the cost-effectiveness of DMTs in people who were diagnosed with CIS in the absence of evidence for RRMS on an MRI scan. We developed a decision analytical model, taking the NHS and PSS perspective, and presented outcomes in terms of cost per QALY gained. We considered six strategies in our analysis, which included treatment with best supportive care in addition to the DMTs available for people with CIS. The base case deterministic results showed that treating people with glatiramer acetate 20 mg (Copaxone) followed by disease modifying treatment on conversion to RRMS dominated the IFN β-1a 30 µg IM once a week (Avonex) and IFN β-1a 44 µg SC three times per week (Rebif) treatment strategies. We found that treatment with IFN β-1b 250 µg SC every other day (Betaferon/Extavia) was extendedly dominated, and although it was cost-effective in comparison to best supportive care, the ICER was higher than that for glatiramer acetate 20 mg SC once daily (Copaxone). Excluding all dominated strategies, the ICER for providing glatiramer acetate 20 mg SC once daily (Copaxone) was approximately £12,900 per QALY gained.

The sensitivity analysis showed that treatment of clinically isolated syndrome with IFN β-1b 250µg SC every other day (Betaferon/Extavia) would also be a cost-effective option if discontinuation rates for all the drug treatments were comparable, or if the decision was evaluated over a short time horizon. The sensitivity analysis did not suggest that treatment with IFN β-1a 30 µg IM once a week (Avonex) or IFN β-1a 44 µg SC three times per week (Rebif) was a cost-effective option in the UK. Results further showed that the

model is likely to be sensitive to the utility associated with the CIS health state and to discontinuation of treatment while in the CIS state.

16.3.2 Strengths and limitations

Our analysis had several strengths. We built a de novo model for CIS, and we were able to incorporate evidence from our systematic review of clinical effectiveness. We also incorporated long-term costs and consequences of progressing to, and receiving disease modifying treatment for RRMS. We also used evidence from the RSS observational cohort to model the effect of conversion to RRMS.

However, our analysis was limited in several important ways. We did not undertake probabilistic sensitivity analysis. Moreover, due to paucity of health related quality of life information in people with CIS, we assumed CIS to be comparable to early phase RRMS. However, we investigated the effect of varying this input parameter on the cost-effectiveness results by 10%, and we found that results still gave ICERs well within expected levels of willingness to pay. Finally, our findings from the clinical effectiveness review relied on a population diagnosed with CIS before the revised 2010 McDonald criteria reclassified many who would have had CIS as in fact having RRMS.

16.3.3 Conclusions

Our cost-effectiveness findings suggest that in people with CIS, it would be cost-effective to start DMTs. We found that of the evaluated DMTs, glatiramer acetate 20 mg SC daily (Copaxone) was the optimal choice. Greater understanding around discontinuation rates of DMTs in CIS patients would be valuable, as it may impact on whether or not IFN β-1b SC 250 μg every other day (Betaferon/Extavia) is also a cost-effective option. These results are presented in the light of some limitations/uncertainty; mainly around the utility values for the clinically isolated syndrome health state, and disutilities associated with adverse events. Our analyses drew on utility values obtained from people with relapsing remitting multiple sclerosis and, due to the complexity of the modeling approach and lack of data, we were unable to quantify this uncertainty by undertaking probabilistic sensitivity analysis. Until more reliable information on utility values become available, these results should be interpreted with caution.

17 DISCUSSION

17.1 *Summary*

17.1.1 Clinical effectiveness

We systematically reviewed and synthesised evidence relating to the effectiveness of interferons and glatiramer acetate within their marketing authorisations for clinically isolated syndrome, relapsing remitting MS and secondary progressive MS. We exhaustively searched databases to update prior high-quality reviews for each of these MS types, and we used standard systematic review methodology to select, appraise and extract data from relevant studies. Our search identified 35 primary studies: five in CIS, 27 in RRMS of which 24 relevant trials reported clinical effectiveness outcomes of interest, and three in SPMS. We synthesised findings from these trials narratively, and where appropriate using pairwise meta-analyses and network meta-analyses. Across MS types, studies were variable in quality. Most studies were manufacturer-sponsored. We also judged that many studies were at high risk of unblinding of participants and personnel due to injection site reactions, with potential implications for blinding of outcome assessors. Many trials, especially of head-to-head comparisons, were open-label.

Clinical effectiveness evidence suggested that IFN and GA were effective for key outcomes and across MS types, and there was little evidence from the NMAs that drugs were superior to others on clinical outcomes. In clinically isolated syndrome, each drug included showed evidence of delaying time to clinically definite MS. In RRMS, drugs showed good evidence of reducing relapse rate, including rate of moderate or severe relapses and in most cases, rate of steroid-treated relapses. Most drugs delayed disability progression confirmed at three months, though findings were less consistent for disability progression confirmed at six months. Finally, in SPMS, all drugs reduced relapse rate, though the network was sparse and relied on three studies. Time to confirmed disability progression at three months was measured in only two studies, which showed variable effects across treatments. We undertook analyses of discontinuation due to AEs in RRMS and SPMS. These analyses, which were intended to be indicative, did not offer evidence that one drug was more likely than another to result in discontinuation due to an AE.

We synthesised findings for additional outcomes in the scope (MS symptoms, health-related quality of life and freedom from disease activity) narratively but were unable to undertake meta-analyses due to heterogeneity, sparsity and poor reporting for these outcomes. Findings suggested a generally beneficial effect on freedom from disease activity, but findings on MS symptoms and health-related quality of life were poorly reported and inconsistent. Additionally, no studies reported discontinuation due to loss of effect attributed to neutralising antibodies.

17.1.2 Cost effectiveness

As part of our assessment of cost effectiveness, we undertook four related work packages. First, we systematically reviewed, appraised and synthesised the recent cost-effectiveness evidence on disease modifying treatments for people with clinically isolated syndrome, and multiple sclerosis. Second, we critically appraised

the Year 10 RSS economic model, including checking the model and reviewing inputs to and assumptions made in the model. Third, we assessed the cost effectiveness of DMTs for the treatment of RRMS. Fourth, we assessed the cost effectiveness of DMTs for the treatment of CIS. We assessed cost effectiveness using a modified RSS model, with clinical effectiveness inputs derived from the Year 10 RSS analyses as the base case. We conducted several additional analyses: 1) using pooled estimates of the effectiveness of on-scheme DMTs from our systematic review of clinical effectiveness, 2) using pooled estimates of the effectiveness of each DMT from our systematic review of clinical effectiveness, and 3) using pooled estimates for the effectiveness of each DMT from company submissions.

We identified ten studies in an RRMS cohort and nine studies in a CIS cohort, which reported evidence on a decision model used to estimate the cost-effectiveness of disease modifying treatment. In general, most studies used appropriate model structures in order to capture/simulate the disease progression. According to best practices for reporting cost-effectiveness analyses, all studies performed satisfactorily in terms of outlining the decision problem, stating the perspective of the analysis, adhering to the scope of the model, and outlining the structural assumptions. However, there were some limitations of these studies. First, we consider the time horizon to be short in some studies, and these analyses may not have captured the full costs and benefits of disease modifying treatments. Second, the choice of model structure in several studies did not accurately reflect disability progression associated with multiple sclerosis. Third, authors did not provide sufficient detail on the meta-analytic methods used to estimate treatment effects of disease modifying treatment or sufficient detail on how treatment effects had been extrapolated beyond trial time horizons.

We considered the RSS model to be appropriate in order to estimate the cost-effectiveness of DMTs compared to best supportive care. The model draws on the best available evidence on disease progression, resource use and costs, and utility values. However, our appraisal highlighted concerns with the RSS model relating to mortality, carers' disutilities, discontinuation rates and how the annualised relapse rate was estimated.

Third, in our base case assessment of cost effectiveness of DMTs for RRMS, our results suggested that it is cost-effective to treat people who have RRMS with DMTs. Using as our base case the RSS model with assumptions relating to mortality and carers' disutilities modified, we found that DMTs were more costly and more effective than best supportive care, with an incremental cost-effectiveness ratio of approximately £27,200 per QALY gained. We also used pooled estimates derived from our clinical effectiveness review for all on-scheme DMTs, which showed that though DMTs were more costly than best supportive care, they also produced more QALYs, and had an incremental cost-effectiveness ratio of approximately £8,100 per QALY. When we compared between each DMT, IFN β-1a SC 125 μg every two weeks (Plegridy) appeared to be the most cost-effective, but clinical effectiveness estimates for this drug were based on one trial with one year of follow-up. Results from the probabilistic sensitivity analysis conducted on the RSS data showed that at a willingness to pay threshold of £20,000/QALY, DMTs had a 37% probability of being cost-effective.

Fourth, we assessed the cost effectiveness of DMTs for CIS. Our base case analysis suggested that treatment with glatiramer acetate 20 mg SC daily was cost-effective relative to best supportive care at £12,900 per QALY gained, and dominated all other strategies in the base case.

17.2 *Strengths and limitations*

17.2.1 In relation to study search, inclusion and exclusion, and selection

We used a rigorous and exhaustive search to locate primary studies, including by updating high-quality systematic reviews. Additionally we used auditable and transparent methods to include and synthesise studies. Where appropriate, we undertook post hoc sensitivity analyses in our clinical effectiveness to check the robustness of our findings.

A limitation of our work, inherent to all systematic reviews, is publication bias. Methods for detecting publication bias in NMAs are still in development, and we did not have enough studies in any one comparison to test for small-study bias. This may be especially relevant since many of the early trials of IFN and GA for MS were small trials.

Another important limitation was the selective and inconsistent reporting of outcomes. For example, one of the reasons we did not undertake a meta-analysis of time to first relapse estimates is that there was inconsistent and often poor reporting, especially across multiple reports of the same study, which prevented imputation of hazard ratios. This was especially a problem with findings relating to MS symptoms and quality of life in individual trials, where findings were often reported as significance thresholds (e.g. $p<0.05$, or $p>0.05$) without effect magnitude.

Finally, we elected to include only studies and arms of studies examining interventions within their marketing authorisations. That is, we did not include study arms examining additional, non-licenced doses of the study drugs. While this meant that our analysis perhaps more closely represents clinical practice today, it does mean that additional information on the effectiveness of these drugs was not included in the analysis. Moreover, because our scope was limited to IFN and GA, we could not include information from additional newer drugs. This was a limitation in that additional trials would have strengthened the resultant study networks analysed (see below).

17.2.2 In relation to synthesis methods and statistical analyses of clinical effectiveness

For most outcomes, we were able to complement narrative syntheses with pairwise and network meta-analyses, but this was not always possible (e.g. magnitude of EDSS change in RRMS, or relapse severity in SPMS).

Our analyses also had several statistical advantages. In examining the effect of IFN and GA on disability progression, we used time to event outcomes and hazard ratios instead of calculating risk ratios or odds ratios at different follow-up points. Thus, trial findings were reported at their fullest 'maturity'[163] and all relevant data

were included. Though hazard ratios are not immune to selection bias, they may be less likely to depend on the time points chosen in the analysis than relative risks.

Related to our decision to use hazard ratios, we were able to use the full complement of methods to estimate effect sizes from available study-level data. This meant that more studies were included in our analyses than would otherwise have been the case. However, this may also be a limitation in that indirect methods (e.g. integrating underneath the survivor function to estimate cumulative hazard) are not preferable to direct estimates of intervention effects.

Our decision to estimate NMAs with effects for relapse rate, relapse severity and time to confirmed disability progression across time points was justified in that rate ratios for relapses account for person-years, and thus under an assumption of a constant rate should not depend on time to follow-up. Similarly, hazard ratios represent 'instantaneous' risk and thus, under a proportional hazards assumption, should not depend on time to follow-up. But this decision is not without its drawbacks. On the one hand, we were unable to verify empirically whether HRs and RRs were time-varying due to few comparisons on every node of the study networks. On the other hand, we judged that stratifying analyses by time to follow-up would have resulted in excessively sparse networks that would have been difficult to interpret collectively. Thus, our decision to pool study estimates across follow-up times for analyses of clinical outcomes was both a strength and a potential limitation. Notably, we did stratify analyses by time to follow-up in NMAs of discontinuations due to AEs, because we judged that the only feasible estimator in these analyses was the risk ratio.

Finally, one issue inherent to the clinical effectiveness evidence was that different sources of bias were spread differentially throughout the networks. Most notably, trials involving active vs. active comparisons in RRMS were frequently open-label in design. Thus, participants were aware of the drugs they were receiving. This might have posed greater risk for unblinding of outcome assessors than in ostensibly double-blinded trials.

17.2.3 In relation to synthesis methods and statistical analyses of cost effectiveness

One strength of our analysis was the considerable effort made to identify the best available evidence on model input parameters and model structure. In addition, several of our analyses were based on estimates derived from our systematic review and NMAs on clinical effectiveness, which were themselves based on rigorous search and analysis. We also appraised the RSS model and were then able modify asssumptions that we found concerning. Our extensive sensitivity analyses, both deterministic and probabilistic, allowed us to explore a variety of data sources. Finally, we were able to develop a de novo model structure for a hypothetical cohort of people with CIS.

However, one limitation of the analyses undertaken with data from the NMAs is that they at times relied on sparse networks with uneven risk of bias throughout the network. For example, analyses relating to pegylated IFN β-1a 125 μg (Plegridy) relied on one trial that was not connected to any other trials except by a placebo comparator. Thus, any issues with the estimates derived from our review of clinical effectiveness would have been propagated through the analysis of cost effectiveness.

Another limitation was the difficulty of estimating uncertainty for key parameters in the RSS model. In conducting our probabilistic sensitivity analysis based on our modified RSS model, we used uncertainty estimates for the annualised relapse rates derived from the clinical effectiveness review rather than from the estimate in the RSS itself.

Additionally, our findings were restricted to IFN and GA. It is possible that other RRMS or CIS treatments may have better cost effectiveness.

17.2.4 In relation to choice of base case for economic analysis

As noted above, we used as our base case a modified version of the RSS model as our base case. While cost-effectiveness estimates derived from the RSS model and from the review of clinical effectiveness evidence have comparative strengths and weaknesses, we decided on balance that estimates from the RSS model provided the best estimate of cost effectiveness. While the RSS model relied on a historical (i.e. non-contemporaneous) comparator and was thus non-randomised evidence likely prone to selection bias, we believed that the long-term follow-up, relevance to the NHS and to current clinical practice, and rigorous methods used in collecting and reporting data made it the best choice as a base case. In contrast, while the estimates from our review of clinical effectiveness were derived from randomised evidence, the predominantly short-term nature of the included trials, the high risk of other biases (including due to manufacturer sponsorship, and due to open-label active vs. active trials), the imbalance of these risks of bias across the networks of evidence, and the sparseness of evidence for some DMTs raised doubts about its value as a base case. While both sources of evidence were at high risk of bias, we believed that the RSS model best represented a relevant base case for MS treatment in the NHS.

17.3 *In relation to the views of patients and carers*

The submission from the Multiple Sclerosis Society supports the use of DMTs for MS including the use of IFN-β and glatiramer acetate based on the results of the RSS, clinical trial data and research on perspectives gathered by the society. These perspectives included several patient case studies reporting that DMTs had significantly reduced or prevented relapses and symptoms, enabling patients to lead more independent active lifestyles. The treatment had improved their mental health by reducing their fear of future relapses and increasing feelings of confidence and control. The MS Society noted that DMTs promote patient choice by allowing individuals to weigh up lower risk moderate efficacy versus higher risk and higher efficacy treatments. The range of treatment options allows for the differential way MS can affect individuals and their differential responses to DMTs.

The current report supports that DMTs are clinically and cost effective for the treatment of both RRMS and CIS, with glatiramer acetate being most effective for annualised relapse rate.

17.4 *In relation to prior research*

Our findings updated prior reviews, though comparability of findings is limited. As compared to Clerico et al. 2008,[154] the key review we used for CIS, we only included trials reporting IFN and GA as used within their marketing authorisation. We included several trials published after their review (Pakdaman 2007,[171] PreCISe 2009,[172] and REFLEX 2012[173]). We were also able to use NMAs for time to clinically definite MS to examine the relative effectiveness of drugs. Our findings substantially update their review and provide additional evidence of the effectiveness of IFN and GA for CIS.

As compared to Tramacere et al. 2015,[155] which broadly examined immunomodulators and immunosuppressants for RRMS, we only included trials examining IFN and GA against each other and against a no-treatment comparator, and only doses and formulations within marketing authorisation. Because they included studies across drugs and because they used risk ratios as the sole outcome estimator, our analyses and theirs are largely incommensurate. However, our analyses for discontinuation due to AEs agreed with theirs in that neither review suggested any one drug had a significant effect on discontinuation due to AEs relative to placebo.

17.5 *Implications for practice*

We did not include formulations outside the recommended usage in the UK. In addition, our study was specifically designed to exclude the clinical and cost-effectiveness of newer MS treatments such as newer monoclonal antibodies (alemtuzumab, daclizumab). This review should be considered in conjunction with newer NICE and other guidance on the clinical and cost-effectiveness of these agents.

Our findings agree with the ABN guidelines[262] in that the guidelines classify IFN-β and GA as drugs of 'moderate efficacy'. Our analysis does suggest that these drugs are effective in controlling relapse rate and disability progression.

17.6 *Protocol variations*

We originally presented our protocol at a Stakeholder Information Meeting and subsequently registered this protocol in PROSPERO. Our methods as conducted differed slightly from the protocol in the following ways.

In our clinical effectiveness systematic reviews, we did not use data from the RSS as a prior distribution in a Bayesian meta-analysis. This was because of the mismatch between the time to follow-up in the trials and the time to follow-up in the year 10 RSS data, and the different analytic methods used between the trials and the RSS analyses. Subsequently, we did not use a Bayesian methodology in our NMA models. We also decided to exclude trials that only examined IFN or GA doses outside their marketing authorisation. Finally, we did not search the database 'Current Clinical Trials', as this would have duplicated searches already covered.

While these were not strictly variations from our protocol, we subsequently refined our definition of several outcomes. We operationalised relapse severity as rate ratios of relapses graded as moderate or severe, or as rate

ratios of relapses requiring steroid treatment. We also took advice from our clinical consultants and examined combined clinical-MRI outcomes for freedom from disease activity.

17.7 *Recommendations for future research*

One key flaw in the assembled clinical effectiveness evidence was the lack of long-term follow-up. The RSS was designed to collect longer-term observational data in this area, however a large-scale, longitudinal randomised trial comparing active first-line agents would contribute meaningfully towards resolving uncertainty about the relative benefits of different IFN or GA formulations. We note that the submission from the MS Society identified a similar research priority. It may be that using blinded adjudicator panels for relapses and disease progression could attenuate the risk of bias accruing to an open-label trial. Because of this lack of long-term follow-up, DMT trials are generally not informative on whether drugs delay progression to SPMS.

There is also a need to reach consensus on the different stages of MS, the distinctiveness of which are open to question. Related to this, there is a need to understand how changing imaging technologies and changes in clinical practice (e.g. changes in the classification of CIS under new diagnostic criteria) impact diagnosis and management. From an epidemiological perspective, a priority for research should be to understand how and under what circumstances MS progresses through different types (e.g. from CIS to RRMS and then SPMS)? We note that the submission from the MS Society identified a similar research priority. Related to this, there is a need to develop outcomes that meaningfully reflect MS symptoms, such as disability progression. Many have enumerated the issues with the EDSS scale, and it is possible that time to progression sustained at 3 months does not reliably capture disability progression, given variable time in recovery from relapses.

Another priority for research is to focus on patients who are not on the lower end of the EDSS scale. This may be of value for populations with MS as survival and advances in support and aids for those with disabilities improve.

Additionally, valuation of health benefits continues to be a vexing area for MS. This was an issue identified in the original guidance resulting from TA32. One possible way to address this issue is through systematic review and metasynthesis of qualitative studies relating to the lived experience of MS, with particular attention to the dominant clinical features, e.g. relapse and disability progression. This could provide a basis for understanding of relefvant health states and benefits, which more closely matches the preferences and experiences of people living with the target condition.

Finally, above and beyond the population average evidence that DMTs reduce relapse rate, there is a need to understand who responds best to DMTs; especially who does not respond to IFN or GA early on, to enable more targeted therapeutic decisions. Though several trials included in our clinical effectiveness review used subgroup analyses based, for example, on presenting lesions or demographic characteristics, a more fine-grained understanding can help patients and clinicians make better-informed decisions.

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19 **Appendix 1: Searches undertaken for systematic reviews of clinical effectiveness**

1.2 Multiple Sclerosis searches

1.2.1 Review articles checked for both included studies and studies excluded with reasons

Cochrane Reviews: Filippini 2013, Tramacere 2015

Other systematic reviews: Tolley 2015

1.2.2 Medline (Ovid), searched 27/01/2016

Exact database: Ovid MEDLINE(R) 1946 to January Week 2 2016

1	exp Multiple Sclerosis/	46764
2	multiple sclerosis.tw.	49799
3	1 or 2	57188
4	randomized controlled trial.pt.	403450
5	controlled clinical trial.pt.	89937
6	clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/	35683
7	(random* or "controlled trial*" or "clinical trial*" or rct).tw.	873696
8	4 or 5 or 6 or 7	1065585
9	Animals/	5743229
10	Humans/	15593111
11	9 not 10	4140900
12	8 not 11	964542
13	3 and 12	4921
14	(metaanalys* or "meta analys*" or "meta-analys*").tw.	69140
15	"systematic* review*".mp.	61461
16	meta analysis.pt.	60117
17	14 or 15 or 16	122687
18	3 and 17	635

19	limit 3 to systematic reviews	1136
20	18 or 19	1233
21	13 or 20	5694
22	limit 21 to yr="2012 -Current"	1545

1.2.3 Medline In-Process & Other Non-Indexed Citations (Ovid), searched 27/01/2016

Actual database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 26, 2016

1	multiple sclerosis.tw.	4892
2	(random* or "controlled trial*" or "clinical trial*" or rct).tw.	108317
3	1 and 2	610
4	(metaanalys* or "meta analys*" or "meta-analys*").tw.	14094
5	"systematic* review*".tw.	15189
6	4 or 5	23570
7	1 and 6	118
8	3 or 7	684
9	limit 8 to yr="2012 -Current"	563

1.2.4 Embase (Ovid), searched 27/01/2016

Actual database: Embase 1974 to 2016 Week 04

1	*multiple sclerosis/	64389
2	multiple sclerosis.tw.	80240
3	1 or 2	87466
4	randomized controlled trial/	392971
5	(random* or "controlled trial*" or "clinical trial*" or rct).tw.	1306964
6	4 or 5	1388801

7	3 and 6	8813
8	meta analysis/	103317
9	(metaanalys* or "meta analys*" or "meta-analys*").tw.	110582
10	"systematic review"/	100520
11	"systematic* review*".tw.	96391
12	8 or 9 or 10 or 11	222654
13	3 and 12	1280
14	7 or 13	9616
15	limit 14 to yr="2012 -Current"	4527
16	limit 15 to (conference abstract or conference paper or conference proceeding)	2363
17	15 not 16	2164

1.2.5 Cochrane Library (Wiley), searched 27/01/2016

ID	Search	Hits
#1	MeSH descriptor: [Multiple Sclerosis] explode all trees	1916
#2	multiple sclerosis:ti,ab,kw (Word variations have been searched)	4921
#3	#1 or #2	4925
#4	#1 or #2 Publication Year from 2012 to 2016	1861

Distribution of results from Cochrane Library search:

- Cochrane Reviews (44)
  - Reviews (39)
  - Protocols (5)
- Other Reviews (DARE) (60)
- Trials (CENTRAL) (1702)
- Methods Studies (0)
- Technology Assessments (HTA Database) (28)
- Economic Evaluations (27)
- Cochrane Groups (0)

1.2.6 Science Citation Index (Web of Knowledge), searched 27/01/2016

# 11	3,248	#9 not #10

		Indexes=SCI-EXPANDED Timespan=All years
# 10	237	(#9) *AND* DOCUMENT TYPES: (Meeting Abstract OR Proceedings Paper) *Indexes=SCI-EXPANDED Timespan=All years*
# 9	3,485	#8 *Indexes=SCI-EXPANDED Timespan=2012-2016*
# 8	9,263	#7 OR #6 *Indexes=SCI-EXPANDED Timespan=All years*
# 7	1,326	#5 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 6	8,425	#2 AND #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 5	216,848	#4 OR #3 *Indexes=SCI-EXPANDED Timespan=All years*
# 4	166,410	TS=(metaanalys* or meta-analys* or (meta NEAR/1 analys*)) *Indexes=SCI-EXPANDED Timespan=All years*
# 3	80,440	TS=(systematic* NEAR/1 review*) *Indexes=SCI-EXPANDED Timespan=All years*
# 2	1,388,789	TS=(random* or (clinical NEAR/1 trial*) or (controlled NEAR/1 trial*) or rct) *Indexes=SCI-EXPANDED Timespan=All years*
# 1	85,913	TS="multiple sclerosis" *Indexes=SCI-EXPANDED Timespan=All years*

1.2.7 UKCRN, searched 27/01/2016

Search:

Keyword: multiple sclerosis

AND

Status: closed

AND

Study Design: Interventional

Total: 41

1.2.8 Cochrane MS group register of trials, searched 26/02/2016

Keywords

(interferon*) OR (interferon beta) OR (beta-1 interferon) OR (beta 1 interferon) OR (interferon beta-1*) OR (rebif) OR (avonex) OR (Betaseron) OR (beta-seron) OR (betaferon) OR (beta-IFN-1*) OR (interferon beta-1*) OR (Interferon-beta*) OR (interferon beta*) OR (recombinant interferon beta-1*) OR (beta-1a interferon) OR (beta 1a interferon) OR (interferon beta-1a) OR (beta 1b interferon) OR (interferon beta1b) OR (IFNb-1b) OR (IFNbeta-1b) OR (interferon beta-1b) OR (copolymer-1) OR (cop-1) OR (copaxone) OR (glatiramer acetate) OR (cpx) OR (cop1) OR (copolymer) OR (glatiramer) OR (polyethylene glycol-interferon-beta-1a) OR (PEG IFN-beta-1a) OR (Pegylated interferon beta-1a) OR (Ocrelizumab)

AND

(relapsing remitting) OR (relapsing-remitting) OR (remitting-relapsing) OR (remitting relapsing) OR (secondary progressive)

Total: 265

1.3 Clinically Isolated Syndrome searches

1.3.1 Review articles checked for included studies and studies excluded with reasons

Cochrane Reviews: Clerico 2008

1.3.2 Medline (Ovid), searched 09/02/2016

Exact database: Ovid MEDLINE(R) 1946 to January Week 4 2016

1	Demyelinating Diseases/	10446
2	Myelitis, Transverse/	1153
3	exp Optic Neuritis/	6737
4	Encephalomyelitis, Acute Disseminated/	1689
5	Demyelinating Autoimmune Diseases, CNS/	316
6	demyelinating disease*.tw.	4725
7	transverse myelitis.tw.	1356
8	neuromyelitis optica.tw.	1735
9	optic neuritis.tw.	3792
10	acute disseminated encephalomyelitis.tw.	1098

11	devic.tw.	107
12	ADEM.tw.	574
13	demyelinating disorder.tw.	335
14	clinically isolated syndrome.tw.	644
15	first demyelinating event.tw.	68
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	24564
17	randomized controlled trial.pt.	404260
18	(random* or "controlled trial*" or "clinical trial*" or rct).tw.	875933
19	17 or 18	975513
20	(metaanalys* or "meta analys*" or "meta-analys*").tw.	69583
21	"systematic* review*".mp.	61879
22	meta analysis.pt.	60490
23	20 or 21 or 22	123386
24	16 and 19	661
25	16 and 23	74
26	24 or 25	713

1.3.3 Medline In-Process & Other Non-Indexed Citations (Ovid), searched 09/02/2016

Actual database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations February 08, 2016

1	demyelinating disease*.tw.	405
2	transverse myelitis.tw.	148
3	neuromyelitis optica.tw.	317
4	optic neuritis.tw.	356
5	acute disseminated encephalomyelitis.tw.	128

6	devic.tw.	6
7	ADEM.tw.	83
8	demyelinating disorder.tw.	55
9	clinically isolated syndrome.tw.	115
10	first demyelinating event.tw.	6
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	1249
12	(random* or "controlled trial*" or "clinical trial*" or rct).tw.	108853
13	(metaanalys* or "meta analys*" or "meta-analys*").tw.	14202
14	"systematic* review*".tw.	15358
15	13 or 14	23763
16	11 and 12	63
17	11 and 15	17
18	16 or 17	73

1.3.4 Embase (Ovid), searched 09/02/2016

Actual database: Embase 1974 to 2016 Week 06

1	demyelinating disease/	12216
2	myelitis/	6771
3	optic neuritis/	6979
4	acute disseminated encephalomyelitis/	1378
5	myelooptic neuropathy/	4897
6	demyelinating disease*.tw.	7443
7	transverse myelitis.tw.	2462
8	neuromyelitis optica.tw.	4162

9	optic neuritis.tw.	6551
10	acute disseminated encephalomyelitis.tw.	1762
11	devic.tw.	229
12	ADEM.tw.	1211
13	demyelinating disorder.tw.	624
14	clinically isolated syndrome.tw.	1758
15	first demyelinating event.tw.	159
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	34739
17	randomized controlled trial/	394252
18	(random* or "controlled trial*" or "clinical trial*" or rct).tw.	1311256
19	17 or 18	1393301
20	meta analysis/	103826
21	(metaanalys* or "meta analys*" or "meta-analys*").tw.	111288
22	"systematic review"/	101172
23	"systematic* review*".tw.	97114
24	20 or 21 or 22 or 23	223913
25	16 and 19	1706
26	16 and 24	322
27	25 or 26	1914
28	limit 27 to (conference abstract or conference paper or conference proceeding or "conference review")	493
29	27 not 28	1421
30	limit 29 to human	1340
31	limit 29 to animals	59
32	31 not 30	59

33	29 not 32	1362

1.3.5 Cochrane Library (Wiley), searched 09/02/2016

ID	Search	Hits
#1	MeSH descriptor: [Multiple Sclerosis] explode all trees	2125
#2	multiple sclerosis:ti,ab,kw (Word variations have been searched)	5081
#3	#1 or #2	5081
#4	first or early or "clinically isolated":ti,ab,kw (Word variations have been searched)	166444
#5	#3 and #4	1037
#6	MeSH descriptor: [Demyelinating Diseases] this term only	71
#7	MeSH descriptor: [Myelitis, Transverse] this term only	6
#8	MeSH descriptor: [Optic Neuritis] explode all trees	95
#9	MeSH descriptor: [Encephalomyelitis, Acute Disseminated] this term only	3
#10	MeSH descriptor: [Demyelinating Autoimmune Diseases, CNS] this term only	2
#11	demyelinating next disease*:ti,ab,kw (Word variations have been searched)	186
#12	transverse myelitis:ti,ab,kw (Word variations have been searched)	14
#13	neuromyelitis optica:ti,ab,kw (Word variations have been searched)	20
#14	optic neuritis:ti,ab,kw (Word variations have been searched)	220
#15	acute disseminated encephalomyelitis:ti,ab,kw (Word variations have been searched)	13
#16	devic:ti,ab,kw (Word variations have been searched)	2
#17	ADEM:ti,ab,kw (Word variations have been searched)	4
#18	demyelinating disorder:ti,ab,kw (Word variations have been searched)	49
#19	clinically isolated syndrome:ti,ab,kw (Word variations have been searched)	114
#20	first demyelinating event:ti,ab,kw (Word variations have been searched)	72
#21	single demyelinating event:ti,ab,kw (Word variations have been searched)	9
#22	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21	1436

Distribution of results from Cochrane Library search:

- Cochrane Reviews (41)

- Other Reviews (8)
- Trials (1369)
- Methods Studies (4)
- Technology Assessments (6)
- Economic Evaluations (8)
- Cochrane Groups (0)

1.3.6 Science Citation Index (Web of Knowledge), searched 10/02/2016

# 19	1,030	#17 NOT #18 Indexes=SCI-EXPANDED Timespan=All years
# 18	93	(#17) AND DOCUMENT TYPES: (Meeting Abstract OR Proceedings Paper) Indexes=SCI-EXPANDED Timespan=All years
# 17	1,123	#16 OR #15 Indexes=SCI-EXPANDED Timespan=All years
# 16	122	#14 AND #10 Indexes=SCI-EXPANDED Timespan=All years
# 15	1,039	#11 AND #10 Indexes=SCI-EXPANDED Timespan=All years
# 14	216,848	#13 OR #12 Indexes=SCI-EXPANDED Timespan=All years
# 13	167,718	TS=(metaanalys* or meta-analys* or (meta NEAR/1 analys*)) Indexes=SCI-EXPANDED Timespan=All years
# 12	80,440	TS=(systematic* NEAR/1 review*) Indexes=SCI-EXPANDED Timespan=All years
# 11	1,393,569	TS=(random* or (clinical NEAR/1 trial*) or (controlled NEAR/1 trial*) or rct) Indexes=SCI-EXPANDED Timespan=All years
# 10	16,869	#9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 Indexes=SCI-EXPANDED Timespan=All years
# 9	96	TS="first demyelinating event" Indexes=SCI-EXPANDED Timespan=All years
# 8	1,195	TS="clinically isolated syndrome" Indexes=SCI-EXPANDED Timespan=All years
# 7	687	TS="ADEM" Indexes=SCI-EXPANDED Timespan=All years
# 6	462	TS="devic" Indexes=SCI-EXPANDED Timespan=All years

# 5	1,596	TS=("acute disseminated" NEAR/1 encephalomyelitis) Indexes=SCI-EXPANDED Timespan=All years
# 4	3,531	TS="neuromyelitis optica" Indexes=SCI-EXPANDED Timespan=All years
# 3	4,584	TS="optic neuritis" Indexes=SCI-EXPANDED Timespan=All years
# 2	1,699	TS=(transverse NEAR/1 myelitis) Indexes=SCI-EXPANDED Timespan=All years
# 1	6,786	TS=(demyelinating NEAR/2 (disease* OR disorder*)) Indexes=SCI-EXPANDED Timespan=All years

1.3.7 Cochrane MS group register of trials, searched 26/02/2016

Keywords for CIS

(interferon*) OR (interferon beta) OR (beta-1 interferon) OR (beta 1 interferon) OR (interferon beta-1*) OR (rebif) OR (avonex) OR (Betaseron) OR (beta-seron) OR (betaferon) OR (beta-IFN-1*) OR (interferon beta-1*) OR (Interferon-beta*) OR (interferon beta*) OR (recombinant interferon beta-1*) OR (beta-1a interferon) OR (beta 1a interferon) OR (interferon beta-1a) OR (beta 1b interferon) OR (interferon beta1b) OR (IFNb-1b) OR (IFNbeta-1b) OR (interferon beta-1b) OR (copolymer-1) OR (cop-1) OR (copaxone) OR (glatiramer acetate) OR (cpx) OR (cop1) OR (copolymer) OR (glatiramer) OR (polyethylene glycol-interferon-beta-1a) OR (PEG IFN-beta-1a) OR (Pegylated interferon beta-1a) OR (Ocrelizumab)

AND

clinically isolated syndrome* OR first demyelinating event* OR first demyelinating episode OR first demyelinating attack OR First event OR first episode OR first clinical episode OR single clinical episodes OR first demyelinating event/* OR clinically isolated syndrome*

Total: 188

1.4 Additional searches for both Multiple Sclerosis and Clinically Isolated Syndrome

1.4.1 ClinicalTrials.gov, searched 03/05/2016

Advanced Search

182 studies found for: Interventional Studies | multiple sclerosis OR clinically isolated syndrome OR CNS demyelinating OR transverse myelitis OR neuromyelitis optica | interferon OR glatiramer OR betaferon OR betaseron OR avonex OR plegridy OR rebif OR extavia OR copaxone | Phase 2, 3, 4

WHO ICTRP, searched 14/07/2016

(Relapsing Remitting Multiple Sclerosis OR RRMS OR clinically isolated syndrome OR CNS demyelinating OR transverse myelitis OR neuromyelitis optica) in the Condition

AND

(interferon OR glatiramer OR betaferon OR betaseron OR avonex OR plegridy OR rebif OR extavia OR copaxone) in the Intervention

588 records for 175 trials found

Websites

	Name (Brand)	**Website address**	**Date searched**
Companies sponsors	Bayer (BETAFERON)	http://www.bayer.co.uk/ http://pharma.bayer.com/	26/04/2016
	Biogen Idec (AVONEX and PLEGRIDY)	https://www.biogen-international.com/ https://www.biogen.uk.com/	28/04/2016
	Merck Serono (REBIF)	http://biopharma.merckgroup.com/en/index.html	
	Novartis (EXTAVIA)	https://www.novartis.com https://www.novartis.co.uk/	28/04/2016
	Teva Pharmaceuticals (COPAXONE)	http://www.tevapharm.com/research_development/ http://www.tevauk.com/	01/05/2016
Patient carer groups	Brain and Spine Foundation	http://www.brainandspine.org.uk	01/05/2016
	Multiple Sclerosis National Therapy Centres	http://www.msntc.org.uk	01/05/2016
	MS UK	http://www.ms-uk.org	01/05/2016
	Multiple Sclerosis Society	https://www.mssociety.org.uk	01/05/2016
	Multiple Sclerosis Trust	https://www.mstrust.org.uk	01/05/2016
	Neurological Alliance	http://www.neural.org.uk	01/05/2016

	The Brain Charity (formally known as Neurosupport)	http://www.thebraincharity.org.uk	01/05/2016
	Sue Ryder	http://www.sueryder.org	01/05/2016
Professional groups	Association of British Neurologists	http://www.theabn.org	01/05/2016
	British Neuropathological Society	http://www.bns.org.uk	01/05/2016
	Institute of Neurology	https://www.ucl.ac.uk/ion https://www.ucl.ac.uk/ion/departments/neuroinflammation http://discovery.ucl.ac.uk	01/05/2016 05/05/2016 10/05/2016
	Primary Care Neurology Society	http://www.p-cns.org.uk	01/05/2016
	Therapists in MS	https://www.mstrust.org.uk/health-professionals/professional-networks/therapists-ms-tims/research	01/05/2016
	United Kingdom Multiple Sclerosis Specialist Nurse Association	http://www.ukmssna.org.uk	01/05/2016
Relevant research groups	Brain Research Trust	http://www.brt.org.uk/research	01/05/2016
	British Neurological Research Trust	http://www.ukscf.org http://www.ukscf.org/about-us/bnrt.html	01/05/2016
	Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System	http://www.cochranelibrary.com http://msrdcns.cochrane.org/our-reviews	01/05/2016
	National Institute for Health Research	http://www.nihr.ac.uk/research/ http://www.nihr.ac.uk/industry/ http://www.nihr.ac.uk/policy-and-standards/	01/05/2016

20 Appendix 2: Sample data extraction sheet for clinical effectiveness reviews

Study acronym/ID:

Name of the reviewer:

Number of publications extracted:

Study details
Study ID (Endnote):
First author surname:
Year of publication:
Country:
Study setting:
Number of centres:
Study period:
Follow up period:
Funding:
Subtypes of MS included:
Definition of CIS used:
Aim of the study
Participants
Inclusion criteria:
Exclusion criteria:
Total number of participants:
Sample attrition/drop out:
Number of participants analysed:
Characteristics of participants
Mean age:
Mean sex:
Race:

EDSS score at baseline: *Relapse rate at baseline:* *Time from diagnosis of MS:* *Other clinical features of MS:*
Intervention (repeat if necessary for multiple intervention arms)
Type of drug: Method of administration: Dose: Frequency: Drug indication as stated:
Best supportive care as described
Outcomes
Primary outcomes: Secondary outcomes: Method of assessing outcomes: If freedom from disease activity is an outcome, how was it defined?: Timing of assessment: Adverse event: Health related quality of life: Yes/No; which measures used?

Number of participants	**Intervention**	**Comparator, if present**
Screened		
Excluded		
Randomised/Included		
Missing participants (people who LTFU during the trial)		
Withdrawals (all who did not complete, including LTFU)		
Patient baseline characteristics	**Intervention:**	**Comparator:**
Age (years)		

Sex		
Race		
EDSS score at baseline		
Relapse rate at baseline		
Time from diagnosis of MS		
Outcome data: relapses, disability	**Intervention**	**Comparator, if present**
Relapse rate		
Severity of relapse		
Disability, including as measured by the Expanded Disability Status Scale		
Freedom from disease activity		
Outcome data: MS symptoms (add rows as necessary)	**Intervention**	**Comparator, if present**
Fatigue		
Visual disturbance		
Cognition		
Outcome data: additional outcomes	**Intervention**	**Comparator, if present**
Mortality		
Health-related quality of life		
Progression to MS (CIS only)		
Discontinuation due to neutralising antibody formation		
Adverse events (add rows as necessary for AEs reported in RCTs)	**Intervention**	**Comparator, if present**

Risk of bias assessment

Random sequence generation	HIGH RISK UNCLEAR LOW RISK
Description in trial	
Allocation concealment	HIGH RISK UNCLEAR LOW RISK
Description in trial	
Blinding of participants and personnel	HIGH RISK UNCLEAR LOW RISK
Description in trial	
Blinding of outcome assessment	HIGH RISK UNCLEAR LOW RISK

Description in trial	
Incomplete outcome data	HIGH RISK UNCLEAR LOW RISK
Description in trial	
Selective reporting	HIGH RISK UNCLEAR LOW RISK
Description in trial	
Other sources of bias	HIGH RISK UNCLEAR LOW RISK
Description in trial	

Authors conclusion
Reviewer's conclusion

21 Appendix 3: Documentation of excluded studies

Table 88: Frequency of reasons for study exclusion in the clinical effectiveness review

Reasons	Number
Conference abstract	10
DMT used with a non-recommended dose regimen	15
Irrelevant comparator/ intervention	58
Irrelevant comparator/ intervention/outcome	1
Irrelevant comparator/ intervention/population	1
Irrelevant comparator/ intervention/ study type	4
Irrelevant comparator/population	5
Irrelevant comparator/population/study type	1
Irrelevant intervention	7
Irrelevant intervention/population	2
Irrelevant intervention/ study type	8
Irrelevant outcome	13
Irrelevant outcome/study type	2
Irrelevant outcome/study type/population	1
Irrelevant population	11
Irrelevant population/outcomes	1
Irrelevant population/study type	7
Irrelevant study type	24
No results are provided, refers to results from a conference abstract	1
Not a primary research study	3
Not English language	1
Protocol only with no results	15
Systematic reviews that didn't enable to locate further primary studies	18
Study evaluating a treatment-switch strategy	1
Use of an unlicensed drug formulation	1
Total	**211**

Table 89: Studies excluded from the clinical effectiveness review with reasons

Reference	Reason for exclusion
(2008) "Glatiramer acetate (Copaxone) for a single demyelinating event with an active inflammatory process (Structured abstract)." Health Technology Assessment Database.	Not a primary research study
(2011) "Laquinimod for multiple sclerosis: relapsing-remitting - first or second line (Structured abstract)." Health Technology Assessment Database.	Not a primary research study
(2011) "Teriflunomide for relapsing multiple sclerosis (MS) - first line (Structured abstract)." Health Technology Assessment Database.	Not a primary research study
Above trial (Bayer) NCT 00206648	Study evaluating a treatment-switch strategy
Aggarwal, S., S. Kumar and H. Topaloglu (2015). "Comparison of Network Meta-Analysis and Traditional Meta-Analysis for Prevention of Relapses In Multiple Sclerosis." Value in Health 18(7): A660.	Conference abstract
Agius, M., X. Meng, P. Chin, A. Grinspan and R. Hashmonay (2014). "Fingolimod therapy in early multiple sclerosis: an efficacy analysis of the TRANSFORMS and FREEDOMS studies by time since first symptom." CNS Neuroscience & Therapeutics 20(5): 446-451.	Irrelevant comparator/ intervention
Aivo, J., B. M. Lindsrom and M. Soilu-Hanninen (2012). "A randomised, double-blind, placebo-controlled trial with vitamin D3 in MS: Subgroup analysis of patients with baseline disease activity despite interferon treatment." Multiple Sclerosis International (no pagination)(802796).	Irrelevant comparator/ intervention
Andersen, O., Elovaara, I., Farkkila, M., Hansen, H. J., Mellgren, S. I., Myhr, K. M., . . . Soelberg Sorensen, P. (2004). Multicentre, randomised, double blind, placebo controlled, phase III study of weekly, low dose, subcutaneous interferon beta-1a in secondary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry, 75(5), 706-710.	DMT used with a non-recommended dose regimen
Andersen, O., I. Elovaara, M. Färkkilä, H. J. Hansen, S. I. Mellgren, K. M. Myhr, M. Sandberg-Wollheim and P. Soelberg Sørensen (2004) "Multicentre, randomised, double blind, placebo controlled, phase III study of weekly, low dose, subcutaneous interferon beta-1a in secondary progressive multiple sclerosis." Journal of neurology, neurosurgery, and psychiatry 75, 706-710.	DMT used with a non-recommended dose regimen
Anderson, G., D. Meyer, C. E. Herrman, C. Sheppard, R. Murray, E. J. Fox, J. Mathena, J. Conner and P. O. Buck (2010) "Tolerability and safety of novel half milliliter formulation of glatiramer acetate for subcutaneous injection: an open-label, multicenter, randomized comparative study." Journal of neurology 257, 1917-1923 DOI: 10.1007/s00415-010-5779-x.	Use of an unlicensed drug formulation
Anonymous (1997). "Visual function 5 years after optic neuritis: experience of the Optic Neuritis Treatment Trial. The Optic Neuritis Study Group." Archives of Ophthalmology 115(12): 1545-1552.	Irrelevant comparator/ intervention
Anonymous (2001). "Early administration of interferon-beta-1a in multiple sclerosis." European Journal of Pediatrics 160(2): 135-136.	Irrelevant study type

Anonymous (2002). "Baseline MRI characteristics of patients at high risk for multiple sclerosis: results from the CHAMPS trial. Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study." Multiple Sclerosis 8(4): 330-338.	Irrelevant outcome
Anonymous (2010) "Developing Neuroprotection and Repair Strategies in MS: Phase IIa Randomized, Controlled Trial of Minocycline in Acute Optic Neuritis (ON)." ClinicalTrials Gov, National Institutes of Health [http://www clinicaltrials gov].	Irrelevant intervention
Arnold, D. L., S. Narayanan and S. Antel (2013). "Neuroprotection with glatiramer acetate: evidence from the PreCISe trial." Journal of Neurology 260(7): 1901-1906.	Irrelevant outcome
Ashtari, F., & Savoj, M. R. (2011). Effects of low dose methotrexate on relapsing-remitting multiple sclerosis in comparison to Interferon beta-1alpha: A randomized controlled trial. J Res Med Sci, 16(4), 457-462.	Irrelevant intervention
Balak, D. M., G. J. Hengstman, A. Cakmak and H. B. Thio (2012). "Cutaneous adverse events associated with disease-modifying treatment in multiple sclerosis: a systematic review." Multiple Sclerosis 18(12): 1705-1717.	SRs that didn't enable to locate further primary studies
Balcer, L. J., S. L. Galetta, P. A. Calabresi, C. Confavreux, G. Giovannoni, E. Havrdova, M. Hutchinson, L. Kappos, F. D. Lublin, D. H. Miller, P. W. O'Connor, J. T. Phillips, C. H. Polman, E. W. Radue, R. A. Rudick, W. H. Stuart, A. Wajgt, B. Weinstock-Guttman, D. R. Wynn, F. Lynn, M. A. Panzara, Affirm and S. Investigators (2007). "Natalizumab reduces visual loss in patients with relapsing multiple sclerosis." Neurology 68(16): 1299-1304.	Irrelevant comparator/ intervention
Bandari, D., D. Wynn, T. Miller, B. Singer, S. Wray, R. Bennett, B. Hayward, F. Dangond and L. S. G. RebiQo (2013). "Rebif() Quality of Life (RebiQoL): A randomized, multicenter, Phase IIIb study evaluating quality-of-life measures in patients receiving the serum-free formulation of subcutaneous interferon beta-1a for the treatment of relapsing forms of multiple sclerosis." Multiple Sclerosis and Related Disorders 2(1): 45-56.	Irrelevant comparator/ intervention
Barkhof, F., C. H. Polman, E. W. Radue, L. Kappos, M. S. Freedman, G. Edan, H. P. Hartung, D. H. Miller, X. Montalban, P. Poppe, M. de Vos, F. Lasri, L. Bauer, S. Dahms, K. Wagner, C. Pohl and R. Sandbrink (2007). "Magnetic resonance imaging effects of interferon beta-1b in the BENEFIT study: integrated 2-year results." Archives of Neurology 64(9): 1292-1298.	Irrelevant outcome
Barkhof, F., M. Rocca, G. Francis, J. H. Van Waesberghe, B. M. Uitdehaag, O. R. Hommes, H. P. Hartung, L. Durelli, G. Edan, O. Fernandez, P. Seeldrayers, P. Sorensen, S. Margrie, M. Rovaris, G. Comi, M. Filippi and G. Early Treatment of Multiple Sclerosis Study (2003). "Validation of diagnostic magnetic resonance imaging criteria for multiple sclerosis and response to interferon beta1a." Annals of Neurology 53(6): 718-724.	DMT used with a non-recommended dose regimen
Beck, R. W. (1995). "The optic neuritis treatment trial: three-year follow-up results." Archives of Ophthalmology 113(2): 136-137.	Irrelevant comparator /intervention/ study type
Beck, R. W. and J. D. Trobe (1995). "The Optic Neuritis Treatment Trial. Putting the results in perspective. The Optic Neuritis Study Group." Journal of Neuro-Ophthalmology 15(3): 131-135.	Irrelevant comparator/ intervention
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Brex, P. A., P. D. Molyneux, P. Smiddy, F. Barkhof, M. Filippi, T. A. Yousry, D. Hahn, Y. Rolland, O. Salonen, C. Pozzilli, C. H. Polman, A. J. Thompson, L. Kappos and D. H. Miller (2001) "The effect of IFNbeta-1b on the evolution of enhancing lesions in secondary progressive MS." Neurology 57, 2185-2190.	Irrelevant outcome
Brunetti, L., M. L. Wagner, M. Maroney and M. Ryan (2013). "Teriflunomide for the treatment of relapsing multiple sclerosis: a review of clinical data." Annals of Pharmacotherapy 47(9): 1153-1160.	Irrelevant intervention/ study type
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Chinea Martinez, A. R., J. Correale, P. K. Coyle, X. Meng and N. Tenenbaum (2014). "Efficacy and safety of fingolimod in Hispanic patients with multiple sclerosis: pooled clinical trial analyses." Advances in Therapy 31(10): 1072-1081.	Irrelevant comparator/ intervention
Clerico, M., G. Contessa and L. Durelli (2007). "Interferon-beta1a for the treatment of multiple sclerosis." Expert Opinion on Biological Therapy 7(4): 535-542.	Irrelevant study type
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Cohen, J. A., A. J. Coles, D. L. Arnold, C. Confavreux, E. J. Fox, H. P. Hartung, E. Havrdova, K. W. Selmaj, H. L. Weiner, E. Fisher, V. V. Brinar, G. Giovannoni, M. Stojanovic, B. I. Ertik, S. L. Lake, D. H. Margolin, M. A. Panzara, D. A. Compston and CARE-MS I investigators (2012). "Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial." Lancet 380(9856): 1819-1828.	Irrelevant comparator/ intervention
Cohen, J. A., Barkhof, F., Comi, G., Hartung, H. P., Khatri, B. O., Montalban, X., . . . Kappos, L. (2010). Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med, 362(5), 402-415. doi: 10.1056/NEJMoa0907839	Irrelevant comparator/ intervention

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Cohen, J. A., F. Barkhof, G. Comi, G. Izquierdo, B. Khatri, X. Montalban, J. Pelletier, B. Eckert, D. A. Haring and G. Francis (2013). "Fingolimod versus intramuscular interferon in patient subgroups from TRANSFORMS." Journal of Neurology 260(8): 2023-2032.	Irrelevant comparator/ intervention
Cohen, J. A., G. R. Cutter, J. S. Fischer, A. D. Goodman, F. R. Heidenreich, M. F. Kooijmans, A. W. Sandrock, R. A. Rudick, J. H. Simon, N. A. Simonian, E. C. Tsao and J. N. Whitaker (2002) "Benefit of interferon beta-1a on MSFC progression in secondary progressive MS." Neurology 59, 679-687.	DMT used with a non-recommended dose regimen
Cohen, J. A., G. R. Cutter, J. S. Fischer, A. D. Goodman, F. R. Heidenreich, M. F. Kooijmans, A. W. Sandrock, R. A. Rudick, J. H. Simon, N. A. Simonian, E. C. Tsao and J. N. Whitaker (2002) "Benefit of interferon beta-1a on MSFC progression in secondary progressive MS." Neurology 59, 679-687.	DMT used with a non-recommended dose regimen
Cohen, J. A., M. Rovaris, A. D. Goodman, D. Ladkani, D. Wynn and M. Filippi (2007) "Randomized, double-blind, dose-comparison study of glatiramer acetate in relapsing-remitting MS." Neurology 68, 939-944 DOI: 10.1212/01.wnl.0000257109.61671.06.	Irrelevant comparator/ intervention/ population
Coles, A. J., C. L. Twyman, D. L. Arnold, J. A. Cohen, C. Confavreux, E. J. Fox, H. P. Hartung, E. Havrdova, K. W. Selmaj, H. L. Weiner, T. Miller, E. Fisher, R. Sandbrink, S. L. Lake, D. H. Margolin, P. Oyuela, M. A. Panzara, D. A. Compston and CARE-MS II investigators (2012). "Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial." Lancet 380(9856): 1829-1839.	Irrelevant comparator/ intervention
Coles, A. J., Compston, D. A., Selmaj, K. W., Lake, S. L., Moran, S., Margolin, D. H., . . . Tandon, P. K. (2008). Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med, 359(17), 1786-1801. doi: 10.1056/NEJMoa0802670	Irrelevant comparator/ intervention
Coles, A. J., D. A. Compston, K. W. Selmaj, S. L. Lake, S. Moran, D. H. Margolin, K. Norris and P. K. Tandon (2008) "Alemtuzumab vs. interferon beta-1a in early multiple sclerosis." The New England journal of medicine 359, 1786-1801 DOI: 10.1056/NEJMoa0802670.	Irrelevant comparator/ intervention
Coles, A. J., E. Fox, A. Vladic, S. K. Gazda, V. Brinar, K. W. Selmaj, A. D. Bass, D. R. Wynn, D. H. Margolin, S. L. Lake, S. Moran, J. Palmer, M. S. Smith and D. A. Compston (2011) "Alemtuzumab versus interferon ?-1a in early relapsing-remitting multiple sclerosis: post-hoc and subset analyses of clinical efficacy outcomes." The Lancet. Neurology 10, 338-348 DOI: 10.1016/S1474-4422(11)70020-5.	Irrelevant comparator/ population
Coles, A. J., E. Fox, A. Vladic, S. K. Gazda, V. Brinar, K. W. Selmaj, A. Skoromets, I. Stolyarov, A. Bass, H. Sullivan, D. H. Margolin, S. L. Lake, S. Moran, J. Palmer, M. S. Smith and D. A. Compston (2012). "Alemtuzumab more effective than interferon beta-1a at 5-year follow-up of CAMMS223 clinical trial." Neurology 78(14): 1069-1078.	Irrelevant comparator/ intervention
Coles, A. J., Twyman, C. L., Arnold, D. L., Cohen, J. A., Confavreux, C., Fox, E. J., . . . investigators, C.-M. I. (2012). Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet, 380(9856), 1829-1839. doi: http://dx.doi.org/10.1016/S0140-6736(12)61768-1	Irrelevant comparator/ intervention

Comi, G., F. Barkhof, L. Durelli, G. Edan, O. Fernandez, M. Filippi, H. P. Hartung, O. R. Hommes, P. Seeldrayers and P. Soelberg-Sorensen (1995). "Early treatment of multiple sclerosis with Rebif (recombinant human interferon beta): design of the study." Multiple Sclerosis 1 Suppl 1: S24-27.	Protocol only with no results
Comi, G., Filippi, M., Barkhof, F., Durelli, L., Edan, G., Fernandez, O., . . . Hommes, O. R. (2001). Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. Lancet, 357(9268), 1576-1582.	DMT used with a non-recommended dose regimen
Comi, G., M. Filippi, F. Barkhof, L. Durelli, G. Edan, O. Fernández, H. Hartung, P. Seeldrayers, P. S. Sørensen, M. Rovaris, V. Martinelli and O. R. Hommes (2001) "Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study." Lancet (London, England) 357, 1576-1582.	DMT used with a non-recommended dose regimen
Comi, G., P. O'Connor, X. Montalban, J. Antel, E. W. Radue, G. Karlsson, H. Pohlmann, S. Aradhye and L. Kappos (2010) "Phase II study of oral fingolimod (FTY720) in multiple sclerosis: 3-year results." Multiple sclerosis (Houndmills, Basingstoke, England) 16, 197-207 DOI: 10.1177/1352458509357065.	Irrelevant comparator/ intervention
Comi, G., J. A. Cohen, D. L. Arnold, D. Wynn and M. Filippi (2011) "Phase III dose-comparison study of glatiramer acetate for multiple sclerosis." Annals of neurology 69, 75-82 DOI: 10.1002/ana.22316.	Irrelevant comparator/ intervention
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Daniels, G. H., A. Vladic, V. Brinar, I. Zavalishin, W. Valente, P. Oyuela, J. Palmer, D. H. Margolin and J. Hollenstein (2014). "Alemtuzumab-related thyroid dysfunction in a phase 2 trial of patients with relapsing-remitting multiple sclerosis." Journal of Clinical Endocrinology & Metabolism 99(1): 80-89.	Irrelevant comparator/ intervention
De Stefano, N., G. Comi, L. Kappos, M. S. Freedman, C. H. Polman, B. M. Uitdehaag, B. Hennessy, F. Casset-Semanaz, L. Lehr, B. Stubinski, D. L. Jack and F. Barkhof (2014). "Efficacy of subcutaneous interferon beta-1a on MRI outcomes in a randomised controlled trial of patients with clinically isolated syndromes." Journal of Neurology, Neurosurgery & Psychiatry 85(6): 647-653.	Irrelevant outcome
De Stefano N, Curtin F, Stubinski B, Blevins G, Drulovic J, Issard D, Shotekov P, Gasperini C; IMPROVE Study Investigators. Rapid benefits of a new formulation of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis. Mult Scler. 2010 Jul;16(7):888-92.	Irrelevant outcome
Deisenhammer, F. and H. Hegen (2012). "Alemtuzumab more effective than interferon beta-1a at 5-year follow-up of CAMMS223 clinical trial." Neurology 79(10): 1071-1072.	Irrelevant study type
Del Santo, F., D. Maratea, V. Fadda, S. Trippoli and A. Messori (2012). "Treatments for relapsing-remitting multiple sclerosis: summarising current information by network meta-analysis." European Journal of Clinical Pharmacology 68(4): 441-448.	SRs that didn't enable to locate further primary studies

Edan, G., L. Kappos, X. Montalban, C. H. Polman, M. S. Freedman, H. P. Hartung, D. Miller, F. Barkhof, J. Herrmann, V. Lanius, B. Stemper, C. Pohl, R. Sandbrink, D. Pleimes and B. S. Group (2014). "Long-term impact of interferon beta-1b in patients with CIS: 8-year follow-up of BENEFIT." Journal of Neurology, Neurosurgery & Psychiatry 85(11): 1183-1189.	Irrelevant comparator/ population/ study type
Etemadifar, M., Janghorbani, M., & Shaygannejad, V. (2007). Comparison of interferon beta products and azathioprine in the treatment of relapsing-remitting multiple sclerosis. J Neurol, 254(12), 1723-1728. doi: 10.1007/s00415-007-0637-1	Irrelevant comparator/ intervention
Etemadifar, M., M. Janghorbani and V. Shaygannejad (2007) "Comparison of interferon beta products and azathioprine in the treatment of relapsing-remitting multiple sclerosis." Journal of neurology 254, 1723-1728 DOI: 10.1007/s00415-007-0637-1.	Irrelevant comparator/ population
Evidence of interferon beta-1a dose response in relapsing-remitting MS: the OWIMS Study. The Once Weekly Interferon for MS Study Group. (1999). Neurology, 53(4), 679-686.	DMT used with a non-recommended dose regimen
Filippi, M., M. Rovaris, M. Inglese, F. Barkhof, N. Stefano, S. Smith and G. Comi (2004) "Interferon beta-1a for brain tissue loss in patients at presentation with syndromes suggestive of multiple sclerosis: a randomised, double-blind, placebo-controlled trial." Lancet (London, England) 364, 1489-1496 DOI: 10.1016/S0140-6736(04)17271-1.	DMT used with a non-recommended dose regimen
Fox, E., D. Arnold, V. Brinar, J. Cohen, A. Coles and C. Confavreux (2012) "Relapse outcomes with alemtuzumab vs. Rebif(registered trademark) in treatment-naive relapsing-remitting multiple sclerosis (CARE-MS I): Secondary and tertiary endpoints." Neurology 78.	Irrelevant comparator/ intervention
Fox, E., K. Edwards, G. Burch, D. R. Wynn, C. LaGanke, H. Crayton, S. F. Hunter, C. Huffman, E. Kim, L. Pestreich, K. McCague, L. Barbato and E. s. investigators (2014). "Outcomes of switching directly to oral fingolimod from injectable therapies: Results of the randomized, open-label, multicenter, Evaluate Patient OutComes (EPOC) study in relapsing multiple sclerosis." Multiple Sclerosis and Related Disorders 3(5): 607-619.	Irrelevant comparator/ intervention
Fox, R. J., B. A. Cree, J. De Seze, R. Gold, H. P. Hartung, D. Jeffery, L. Kappos, M. Kaufman, X. Montalban, B. Weinstock-Guttman, B. Anderson, A. Natarajan, B. Ticho, P. Duda and Restore (2014). "MS disease activity in RESTORE: a randomized 24-week natalizumab treatment interruption study.[Erratum appears in Neurology. 2015 Feb 24;84(8):862 Note: multiple investigator names added]." Neurology 82(17): 1491-1498.	Irrelevant comparator/ intervention
Fox, R. J., B. A. Cree, J. Sèze, R. Gold, H. P. Hartung, D. Jeffery, L. Kappos, M. Kaufman, X. Montalbán, B. Weinstock-Guttman, B. Anderson, A. Natarajan, B. Ticho, P. Duda and Restore (2014) "MS disease activity in RESTORE: a randomized 24-week natalizumab treatment interruption study." Neurology 82, 1491-1498 DOI: 10.1212/WNL.0000000000000355.	Irrelevant population
Freedman, M. S. (2014). "Evidence for the efficacy of interferon beta-1b in delaying the onset of clinically definite multiple sclerosis in individuals with clinically isolated syndrome." Therapeutic Advances in Neurological Disorders 7(6): 279-288.	Irrelevant intervention/ population
Freedman, M. S., J. S. Wolinsky, B. Wamil, C. Confavreux, G. Comi, L. Kappos, T. P. Olsson, A. Miller, H. Benzerdjeb, H. Li, C. Simonson, P. W. O'Connor, G. Teriflunomide Multiple Sclerosis Trial and M. R. I. A. C. the (2012). "Teriflunomide added to interferon-beta in relapsing multiple sclerosis: a randomized phase II trial." Neurology 78(23): 1877-1885.	Irrelevant intervention

Freedman, M. S., P. Truffinet, G. Comi, L. Kappos, A. E. Miller, T. P. Olsson, M. Benamor, S. Chambers and P. W. O'Connor (2015). "A randomized trial of teriflunomide added to glatiramer acetate in relapsing multiple sclerosis." Multiple Sclerosis Journal - Experimental, Translational and Clinical 1: 1-10.	Irrelevant intervention
Freedman, M. S., Wolinsky, J. S., Wamil, B., Confavreux, C., Comi, G., Kappos, L., . . . the, M. R. I. A. C. (2012). Teriflunomide added to interferon-beta in relapsing multiple sclerosis: a randomized phase II trial. Neurology, 78(23), 1877-1885. doi: http://dx.doi.org/10.1212/WNL.0b013e318258f7d4	Irrelevant comparator/ intervention
Frohman, E. M., E. Havrdova, F. Lublin, F. Barkhof, A. Achiron, M. K. Sharief, O. Stuve, M. K. Racke, L. Steinman, H. Weiner, M. Olek, R. Zivadinov, J. Corboy, C. Raine, G. Cutter, J. Richert and M. Filippi (2006). "Most patients with multiple sclerosis or a clinically isolated demyelinating syndrome should be treated at the time of diagnosis." Archives of Neurology 63(4): 614-619.	Irrelevant study type
Giovannoni, G., E. Southam and E. Waubant (2012). "Systematic review of disease-modifying therapies to assess unmet needs in multiple sclerosis: tolerability and adherence." Multiple Sclerosis 18(7): 932-946.	SRs that didn't enable to locate further primary studies
Giovannoni, G., G. Comi, S. Cook, K. Rammohan, P. Rieckmann and P. Soelberg-Sorensen (2013) "Safety and efficacy of oral cladribine in patients with relapsing-remitting multiple sclerosis: Results from the 96 week phase IIIB extension trial to the clarity study." Neurology 80.	Irrelevant intervention
Gobbi, C., D. S. Meier, F. Cotton, M. Sintzel, D. Leppert, C. R. Guttmann and C. Zecca (2013). "Interferon beta 1b following natalizumab discontinuation: one year, randomized, prospective, pilot trial." BMC Neurology 13: 101.	Irrelevant comparator/ intervention/ study type
Goodin, D. S., A. T. Reder, G. C. Ebers, G. Cutter, M. Kremenchutzky, J. Oger, D. Langdon, M. Rametta, K. Beckmann, T. M. DeSimone and V. Knappertz (2012). "Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFNbeta-1b trial." Neurology 78(17): 1315-1322.	Irrelevant comparator/ intervention/ study type
Goodin, D. S., G. C. Ebers, G. Cutter, S. D. Cook, T. O'Donnell, A. T. Reder, M. Kremenchutzky, J. Oger, M. Rametta, K. Beckmann and V. Knappertz (2012). "Cause of death in MS: long-term follow-up of a randomised cohort, 21 years after the start of the pivotal IFNbeta-1b study." BMJ Open 2(6).	Irrelevant intervention/ study type
Gotkine, M. (2008) "Neuromyelitis optica and the Optic Neuritis Treatment Trial." Archives of neurology 65, 1545-1546.	Irrelevant study type
Govindappa, K., J. Sathish, K. Park, J. Kirkham and M. Pirmohamed (2015). "Development of interferon beta-neutralising antibodies in multiple sclerosis--a systematic review and meta-analysis." European Journal of Clinical Pharmacology 71(11): 1287-1298.	Irrelevant outcome/ study type
Hadden, R. D., B. Sharrack, S. Bensa, S. E. Soudain and R. A. Hughes (1999). "Randomized trial of interferon beta-1a in chronic inflammatory demyelinating polyradiculoneuropathy." Neurology 53(1): 57-61.	Irrelevant population
Hadjigeorgiou, G. M., C. Doxani, M. Miligkos, P. Ziakas, G. Bakalos, D. Papadimitriou, T. Mprotsis, N. Grigoriadis and E. Zintzaras (2013). "A network meta-analysis of randomized controlled trials for comparing the effectiveness and safety profile of treatments with marketing authorization for relapsing multiple sclerosis." Journal of Clinical Pharmacy & Therapeutics 38(6): 433-439.	SRs that didn't enable to locate further primary studies

Hartung, H. P., M. S. Freedman, C. H. Polman, G. Edan, L. Kappos, D. H. Miller, X. Montalban, F. Barkhof, J. Petkau, R. White, V. Sahajpal, V. Knappertz, K. Beckmann, V. Lanius, R. Sandbrink, C. Pohl and B. S. Group (2011). "Interferon beta-1b-neutralizing antibodies 5 years after clinically isolated syndrome.[Erratum appears in Neurology. 2011 Sep 27;77(13):1317]." Neurology 77(9): 835-843.	Irrelevant study type
Hartung, H., T. Vollmer, D. Arnold, J. Cohen, A. Coles and C. Confavreux (2013) "Alemtuzumab reduces ms disease activity in active relapsing-remitting multiple sclerosis patients who had disease activity on prior therapy." Neurology 80.	Conference abstract
Havrdova, E., G. Giovannoni, D. Stefoski, K. Umans, S. Greenberg and L. Mehta (2013) "Proportion of disease-activity free patients with relapsing-remitting multiple sclerosis following 1 year of treatment with daclizumab high-yield process in the select study." Neurology 80.	Conference abstract
Havrdova, E., Zivadinov, R., Krasensky, J., Dwyer, M. G., Novakova, I., Dolezal, O., . . . Horakova, D. (2009). Randomized study of interferon beta-1a, low-dose azathioprine, and low-dose corticosteroids in multiple sclerosis. Mult Scler, 15(8), 965-976. doi: 10.1177/1352458509105229	Irrelevant comparator/ intervention
Hersh, C. M. and J. A. Cohen (2014). "Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis." Immunotherapy 6(3): 249-259.	Irrelevant study type
Hutchinson, M., R. J. Fox, D. H. Miller, J. T. Phillips, M. Kita, E. Havrdova, J. O'Gorman, R. Zhang, M. Novas, V. Viglietta and K. T. Dawson (2013). "Clinical efficacy of BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: subgroup analyses of the CONFIRM study." Journal of Neurology 260(9): 2286-2296.	SRs that didn't enable to locate further primary studies
Hutchinson, M., R. J. Fox, E. Havrdova, N. C. Kurukulasuriya, S. P. Sarda, S. Agarwal, M. K. Siddiqui, A. Taneja and B. Deniz (2014). "Efficacy and safety of BG-12 (dimethyl fumarate) and other disease-modifying therapies for the treatment of relapsing-remitting multiple sclerosis: a systematic review and mixed treatment comparison." Current Medical Research & Opinion 30(4): 613-627.	SRs that didn't enable to locate further primary studies
Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, Fischer JS, Goodkin DE, Granger CV, Simon JH, et al. A phase III trial of intramuscular recombinant interferon beta as treatment for exacerbating-remitting multiple sclerosis: design and conduct of study and baseline characteristics of patients. Multiple Sclerosis Collaborative Research Group (MSCRG). Mult Scler. 1995 Jun;1(2):118-35. PubMed PMID: 9345462.	Protocol only with no results
Jacobs, L. D., R. W. Beck and J. H. Simon (2001). "Interferon beta-1a prevented the development of clinically definite multiple sclerosis after a first demyelinating event." Evidence-Based Medicine 6(3): 78.	Irrelevant study type
Jacques, F., I. Gaboury, S. Christie and F. Grand'maison (2012). "Combination therapy of interferon Beta-1b and tacrolimus: a pilot safety study." Multiple Sclerosis International 2012: 935921.	Irrelevant comparator/ intervention
Johnson, K. P., B. R. Brooks, C. C. Ford, A. D. Goodman, R. P. Lisak, L. W. Myers, A. A. Pruitt, M. A. Rizzo, J. W. Rose, L. P. Weiner and J. S. Wolinsky (2003) "Glatiramer acetate (Copaxone): comparison of continuous versus delayed therapy in a six-year organized multiple sclerosis trial." Multiple sclerosis (Houndmills, Basingstoke, England) 9, 585-591.	Irrelevant population
Kalincik, T., D. Horakova, O. Dolezal, J. Krasensky, M. Vaneckova, Z. Seidl and E. Havrdova (2012). "Interferon, azathioprine and corticosteroids in multiple sclerosis: 6-year follow-up of the ASA cohort." Clinical Neurology & Neurosurgery 114(7): 940-946.	Irrelevant comparator/ intervention

Kamm, C. P., M. El-Koussy, S. Humpert, O. Findling, F. von Bredow, Y. Burren, G. Schwegler, D. Schott, F. Donati, M. Muller, N. Goebels, F. Muller, J. Slotboom, B. Tettenborn, L. Kappos, Y. Naegelin and H. P. Mattle (2012). "Atorvastatin added to interferon beta for relapsing multiple sclerosis: a randomized controlled trial." Journal of Neurology 259(11): 2401-2413.	Irrelevant comparator/ intervention
Kamm, C. P., M. El-Koussy, S. Humpert, O. Findling, Y. Burren, G. Schwegler, F. Donati, M. Muller, F. Muller, J. Slotboom, L. Kappos, Y. Naegelin, H. P. Mattle and S. S. Group (2014). "Atorvastatin added to interferon beta for relapsing multiple sclerosis: 12-month treatment extension of the randomized multicenter SWABIMS trial." PLoS ONE [Electronic Resource] 9(1): e86663.	Irrelevant comparator/ intervention
Kappos, L., A. Traboulsee, C. Constantinescu, J. P. Erälinna, F. Forrestal, P. Jongen, J. Pollard, M. Sandberg-Wollheim, C. Sindic, B. Stubinski, B. Uitdehaag and D. Li (2006) "Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS." Neurology 67, 944-953 DOI: 10.1212/01.wnl.0000237994.95410.ce.	Irrelevant population/ study type
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Roskell, N. S., E. A. Zimovetz, C. E. Rycroft, B. J. Eckert and D. A. Tyas (2012). "Annualized relapse rate of first-line treatments for multiple sclerosis: a meta-analysis, including indirect comparisons versus fingolimod." Current Medical Research & Opinion 28(5): 767-780.	SRs that didn't enable to locate further primary studies
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Sellner, J., M. Boggild, M. Clanet, R. Q. Hintzen, Z. Illes, X. Montalban, R. A. Du Pasquier, C. H. Polman, P. S. Sorensen and B. Hemmer (2010). "EFNS guidelines on diagnosis and management of neuromyelitis optica." European Journal of Neurology 17(8): 1019-1032.	Irrelevant intervention/ study type
Siddiqui, M. A. A. and K. Wellington (2005). "Intramuscular interferon-beta-1a: In patients at high risk of developing clinically definite multiple sclerosis." CNS Drugs 19(1): 55-61.	Irrelevant study type
Simon, J. H., L. D. Jacobs, M. Campion, K. Wende, N. Simonian, D. L. Cookfair, R. A. Rudick, R. M. Herndon, J. R. Richert, A. M. Salazar, J. J. Alam, J. S. Fischer, D. E. Goodkin, C. V. Granger, M. Lajaunie, A. L. Martens-Davidson, M. Meyer, J. Sheeder, K. Choi, A. L. Scherzinger, D. M. Bartoszak, D. N. Bourdette, J. Braiman, C. M. Brownscheidle and R. H. Whitham (1998) "Magnetic resonance studies of intramuscular interferon beta-1a for relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group." Annals of neurology 43, 79-87 DOI: 10.1002/ana.410430114.	Irrelevant outcome
Soilu-Hanninen, M., J. Aivo, B. M. Lindstrom, I. Elovaara, M. L. Sumelahti, M. Farkkila, P. Tienari, S. Atula, T. Sarasoja, L. Herrala, I. Keskinarkaus, J. Kruger, T. Kallio, M. A. Rocca and M. Filippi (2012). "A randomised, double blind, placebo controlled trial with vitamin D3 as an add on treatment to interferon beta-1b in patients with multiple sclerosis." Journal of Neurology, Neurosurgery & Psychiatry 83(5): 565-571.	Irrelevant comparator/ intervention
Sorensen, P. S., Lisby, S., Grove, R., Derosier, F., Shackelford, S., Havrdova, E., . . . Filippi, M. (2014). Safety and efficacy of ofatumumab in relapsing-remitting multiple sclerosis: a phase 2 study. Neurology, 82(7), 573-581. doi: 10.1212/wnl.0000000000000125	Irrelevant comparator/ intervention
Sormani, M. P., P. Bruzzi, K. Beckmann, K. Wagner, D. H. Miller, L. Kappos and M. Filippi (2003) "MRI metrics as surrogate endpoints for EDSS progression in SPMS patients treated with IFN beta-1b." Neurology 60, 1462-1466.	Irrelevant outcome
St?pie, A., M. Chalimoniuk, D. b. N. Lubina, S. J. Chrapusta, H. Galbo and J. Langfort (2013) "Effects of interferon ?-1a and interferon ?-1b monotherapies on selected serum cytokines and nitrite levels in patients with relapsing-remitting multiple sclerosis: a 3-year longitudinal study." Neuroimmunomodulation 20, 213-222 DOI: 10.1159/000348701.	Irrelevant population/ outcomes
Suhs, K. W., K. Hein, J. R. Pehlke, B. Kasmann-Kellner and R. Diem (2012) "Retinal Nerve Fibre Layer Thinning in Patients with Clinically Isolated Optic Neuritis and Early Treatment with Interferon-Beta." PloS one 7 DOI: 10.1371/journal.pone.0051645.	Irrelevant study type
Tolley, K., M. Hutchinson, X. You, P. Wang, B. Sperling, A. Taneja, M. K. Siddiqui and E. Kinter (2015). "A Network Meta-Analysis of Efficacy and Evaluation of Safety of Subcutaneous Pegylated Interferon Beta-1a versus Other Injectable Therapies for the Treatment of Relapsing-Remitting Multiple Sclerosis." PLoS ONE [Electronic Resource] 10(6): e0127960.	SRs that didn't enable to locate further primary studies
Tsivgoulis, G., A. H. Katsanos, N. Grigoriadis, G. M. Hadjigeorgiou, I. Heliopoulos, C. Kilidireas and K. Voumvourakis (2015). "The effect of disease modifying therapies on brain atrophy in patients with relapsing-remitting multiple sclerosis: a systematic review and meta-analysis." PLoS ONE [Electronic Resource] 10(3): e0116511.	Irrelevant outcome/ study type
Tsivgoulis, G., A. H. Katsanos, N. Grigoriadis, G. M. Hadjigeorgiou, I. Heliopoulos, P. Papathanasopoulos, C. Kilidireas, K. Voumvourakis, E. Dardiotis and Helani (2015). "The Effect of Disease Modifying Therapies on Disease Progression in Patients with Relapsing-Remitting Multiple Sclerosis: A Systematic Review and Meta-Analysis." PLoS ONE [Electronic Resource] 10(12): e0144538.	SRs that didn't enable to locate further primary studies

Tsivgoulis, G., A. H. Katsanos, N. Grigoriadis, G. M. Hadjigeorgiou, I. Heliopoulos, P. Papathanasopoulos, E. Dardiotis, C. Kilidireas, K. Voumvourakis and Helani (2015). "The effect of disease-modifying therapies on brain atrophy in patients with clinically isolated syndrome: a systematic review and meta-analysis." Therapeutic Advances in Neurological Disorders 8(5): 193-202.	Irrelevant outcome/ study type/ population
Vermersch, P., A. Czlonkowska, L. M. Grimaldi, C. Confavreux, G. Comi, L. Kappos, T. P. Olsson, M. Benamor, D. Bauer, P. Truffinet, M. Church, A. E. Miller, J. S. Wolinsky, M. S. Freedman, P. O'Connor and T. T. Group (2014). "Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial." Multiple Sclerosis 20(6): 705-716.	Irrelevant comparator/ intervention
Vermersch, P., Czlonkowska, A., Grimaldi, L. M., Confavreux, C., Comi, G., Kappos, L., . . . Group, T. T. (2014). Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Mult Scler, 20(6), 705-716. doi: http://dx.doi.org/10.1177/1352458513507821	Irrelevant intervention
Vollmer, T. L., P. S. Sorensen, K. Selmaj, F. Zipp, E. Havrdova, J. A. Cohen, N. Sasson, Y. Gilgun-Sherki, D. L. Arnold and B. S. Group (2014). "A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis." Journal of Neurology 261(4): 773-783.	Conference abstract
Vollmer, T., D. Jeffery, D. Goodin, L. Kappos, F. Lublin and E. W. Radue (2013) "Long-term safety of fingolimod in patients with relapsing-remitting multiple sclerosis: Results from phase 3 freedoms II extension study." Neurology 80.	Irrelevant comparator/ intervention
Vollmer, T., H. Panitch, A. Bar-Or, J. Dunn, M. S. Freedman, S. K. Gazda, D. Campagnolo, F. Deutsch and D. L. Arnold (2008) "Glatiramer acetate after induction therapy with mitoxantrone in relapsing multiple sclerosis." Multiple sclerosis (Houndmills, Basingstoke, England) 14, 663-670 DOI: 10.1177/1352458507085759.	Irrelevant comparator/ population
Voskuhl, R. R., H. Wang, T. C. Wu, N. L. Sicotte, K. Nakamura, F. Kurth, N. Itoh, J. Bardens, J. T. Bernard, J. R. Corboy, A. H. Cross, S. Dhib-Jalbut, C. C. Ford, E. M. Frohman, B. Giesser, D. Jacobs, L. H. Kasper, S. Lynch, G. Parry, M. K. Racke, A. T. Reder, J. Rose, D. M. Wingerchuk, A. J. MacKenzie-Graham, D. L. Arnold, C. H. Tseng and R. Elashoff (2016). "Estriol combined with glatiramer acetate for women with relapsing-remitting multiple sclerosis: a randomised, placebo-controlled, phase 2 trial." Lancet Neurology 15(1): 35-46.	Irrelevant comparator/ intervention
Waubant, E., A. H. Maghzi, N. Revirajan, R. Spain, L. Julian, E. M. Mowry, J. Marcus, S. Liu, C. Jin, A. Green, C. E. McCulloch and D. Pelletier (2014). "A randomized controlled phase II trial of riluzole in early multiple sclerosis." Annals of Clinical & Translational Neurology 1(5): 340-347.	Irrelevant comparator/ intervention
Waubant, E., D. Pelletier, M. Mass, J. A. Cohen, M. Kita, A. Cross, A. Bar-Or, T. Vollmer, M. Racke, O. Stuve, S. Schwid, A. Goodman, N. Kachuck, J. Preiningerova, B. Weinstock-Guttman, P. A. Calabresi, A. Miller, M. Mokhtarani, D. Ikle, S. Murphy, H. Kopetskie, L. Ding, E. Rosenberg, C. Spencer, S. S. Zamvil and I. T. N. S. S. Grp (2012). "Randomized controlled trial of atorvastatin in clinically isolated syndrome The STAyCIS study." Neurology 78(15): 1171-1178.	Irrelevant comparator/ intervention
Weinshenker, B. G. (2014). "Review: In relapsing-remitting multiple sclerosis, disease-modifying agents reduce annual relapse rates." Annals of Internal Medicine 160(6): JC5.	Conference abstract
Weinstock-Guttman, B., S. L. Galetta, G. Giovannoni, E. Havrdova, M. Hutchinson, L. Kappos, P. W. O'Connor, J. T. Phillips, C. Polman, W. H. Stuart, F. Lynn and C.	Irrelevant comparator/ intervention

Hotermans (2012). "Additional efficacy endpoints from pivotal natalizumab trials in relapsing-remitting MS." Journal of Neurology 259(5): 898-905.	
Wolinsky, J. S., Narayana, P. A., O'Connor, P., Coyle, P. K., Ford, C., Johnson, K., . . . Ladkani, D. (2007). Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. Ann Neurol, 61(1), 14-24. doi: 10.1002/ana.21079	Irrelevant population
Wolinsky, J. S., P. A. Narayana, P. O'Connor, P. K. Coyle, C. Ford, K. Johnson, A. Miller, L. Pardo, S. Kadosh and D. Ladkani (2007) "Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial." Annals of neurology 61, 14-24 DOI: 10.1002/ana.21079.	Irrelevant population
Wolinsky, J. S., T. E. Borresen, D. W. Dietrich, D. Wynn, Y. Sidi, J. R. Steinerman, V. Knappertz, S. Kolodny and G. S. Group (2015). "GLACIER: An open-label, randomized, multicenter study to assess the safety and tolerability of glatiramer acetate 40 mg three-times weekly versus 20 mg daily in patients with relapsing-remitting multiple sclerosis." Multiple Sclerosis and Related Disorders 4(4): 370-376.	Irrelevant study type
Wynn, D., Kaufman, M., Montalban, X., Vollmer, T., Simon, J., Elkins, J., . . . Rose, J. W. (2010). Daclizumab in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. Lancet Neurol, 9(4), 381-390. doi: 10.1016/s1474-4422(10)70033-8	Irrelevant intervention
Zagmutt, F. J. and C. A. Carroll (2015). "Meta-analysis of adverse events in recent randomized clinical trials for dimethyl fumarate, glatiramer acetate and teriflunomide for the treatment of relapsing forms of multiple sclerosis." International Journal of Neuroscience 125(11): 798-807.	SRs that didn't enable to locate further primary studies
Ziemssen, T., J. Hoffman, R. Apfel and S. Kern (2008) "Effects of glatiramer acetate on fatigue and days of absence from work in first-time treated relapsing-remitting multiple sclerosis." Health and quality of life outcomes 6.	Irrelevant population/ study type
Zintzaras, E., C. Doxani, T. Mprotsis, C. H. Schmid and G. M. Hadjigeorgiou (2012). "Network analysis of randomized controlled trials in multiple sclerosis." Clinical Therapeutics 34(4): 857-869.e859.	SRs that didn't enable to locate further primary studies
Zivadinov, R., M. G. Dwyer, D. P. Ramasamy, M. D. Davis, J. R. Steinerman and O. Khan (2015). "The Effect of Three Times a Week Glatiramer Acetate on Cerebral T1 Hypointense Lesions in Relapsing-Remitting Multiple Sclerosis." Journal of Neuroimaging 25(6): 989-995.	Irrelevant outcome

22 **Appendix 4: Studies included in the clinical effectiveness review with relevant publications**

Study ID	Title	Full article(s) – main	Full article(s) - other
ADVANCE 2014	A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of PEGylated Interferon Beta-1a (BIIB017) in Subjects With Relapsing Multiple Sclerosis	Calabresi 2014[211]	Arnold 2014[212] (MRI), Newsome 2015[213] (HRQoL)
AVANTAGE 2014	Safety Study in Relapsing-remitting Multiple Sclerosis (RRMS) Patients Receiving Betaferon or Rebif	No formal publication, results on company website[180] and ClinicalTrials.gov	
BECOME 2009	Phase IV, Rater-blinded, Randomized Study, Comparing 250 mg of Betaseron With 20 mg of Copaxone in Patients With the Relapsing-remitting(RR) or CIS Forms of ms Using 3 Tesla(3T) Magnetic Resonance Imaging (MRI) With Triple-dose Gadolinium	Cadavid 2009[182]	Cadavid 2011[210]
BENEFIT 2006	The BEtaferon in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) trial	Kappos 2006[169]	Polman 2008[177] (Subgroup analysis), Penner 2012[178] (cognitive performance in CIS)
BEYOND 2009	International, Randomized, Multicenter, Phase IIIb Study in Patients With Relapsing-Remitting Multiple Sclerosis Comparing Over a Treatment Period of at Least 104 Weeks: 1. Double-Blinded Safety, Tolerability, and Efficacy of Betaseron/ Betaferon 250 µg (8 MIU) and Betaseron/-Betaferon 500 µg (16 MIU), Both Given Subcutaneously Every Other Day, and 2. Rater-Blinded Safety, Tolerability, and Efficacy of Betaseron/-Betaferon s.c. Every Other Day With Copaxone 20 mg s.c. Once Daily.	O'Connor 2009[188]	Filippi 2011[276] (Post hoc analysis of MRI scans)
Bornstein 1987	A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis	Bornstein 1987[168]	
BRAVO 2014	A Multinational, Multicenter, Randomized, Parallel-group Study Performed in Subjects With RRMS to Assess the Efficacy, Safety and Tolerability of Laquinimod Over Placebo in a Double-blind Design and a Reference Arm of Interferon β-1a (Avonex®) in a Rater-blinded Design.	Vollmer 2014[196]	
Calabrese 2012	Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing–remitting multiple sclerosis	Calabrese 2012[186]	

CHAMPS 2000	Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis	Jacobs 2000[170]	Beck 2002[174] (Subgroup analysis, CHAMPS 2001[277] (Subgroup of acute optic neuritis), O'Connor 2003[278] (Subgroup analysis), O'Connor 2009[175] (Subgroup analysis)
CombiRx 2013	A Multi-Center, Double-Blind, Randomized Study Comparing the Combined Use of Interferon Beta-1a and Glatiramer Acetate to Either Agent Alone in Patients With Relapsing-Remitting Multiple Sclerosis (CombiRx)	Lublin 2013[189]	Lindsey 2012[279] (protocol)
CONFIRM 2012	A Randomized, Multicenter, Placebo-Controlled and Active Reference (Glatiramer Acetate) Comparison Study to Evaluate the Efficacy and Safety of BG00012 in Subjects With Relapsing-Remitting Multiple Sclerosis	Fox 2012[214]	Kita 2014[280] (HRQoL)
Cop1 MSSG 1995		Johnson 1995[215] (initial findings)	Johnson 1998[216] (final results)
ECGASG 2001	European/Canadian Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of the Effects of Glatiramer Acetate on Magnetic Resonance Imaging–Measured Disease Activity and Burden in Patients with Relapsing Multiple Sclerosis	Comi 2001[217]	
ESG 1998	Placebo-controlled multicentre randomised trial of interferon-1b in treatment of secondary progressive multiple sclerosis	European Study Group on Interferon Beta-1b in secondary progressive MS 1998[220]	Kappos 2001[223] (Final results)
Etemadifar 2006	Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing–remitting multiple sclerosis	Etemadifar 2006[183]	
EVIDENCE 2007	Full Results of the Evidence of Interferon Dose-Response-European North American Comparative Efficacy (EVIDENCE) Study: A Muhicenter, Randomized, Assessor-Blinded Comparison of Low-Dose Weekly Versus High-Dose, High-Frequency Interferon 13-1a for Relapsing Multiple Sclerosis	Schwid 2007[193]	Panitch 2002[191] (comparative results), Panitch 2005[192] (final comparative results), Sandberg-Wollheim 2005[204] (AEs)
GALA 2013	Three Times Weekly Glatiramer Acetate in Relapsing–Remitting Multiple Sclerosis	Khan 2013[219]	
GATE 2015	Multi-centre, Randomized, Double-blind, Placebo-controlled, Parallel-group, 9 Month, Equivalence Trial Comparing the Efficacy and Safety and Tolerability of GTR (Synthon BV) to Copaxone® (Teva) in Subjects With Relapsing Remitting	Cohen 2015[218]	

	Multiple Sclerosis Followed by an Open-label 15 Month GTR Treatment Part Evaluating the Long-term GTR Treatment Effects		
IFNB MSSG 1995	Interferon beta-lb is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial	IFNB Multiple Sclerosis Study Group 1993[207]	IFNB Multiple Sclerosis Study Group 1995[208] (additional data and further details)
IMPROVE 2012	A Two-arm, Randomized, Double-blind, Control Group-compared, Multicenter, Phase IIIb Study With Monthly MRI and Biomarker Assessments to Evaluate the Efficacy, Safety, and Tolerability of Rebif® New Formulation (IFN Beta-1a) in Subjects With Relapsing Remitting Multiple Sclerosis	De Stefano 2012[205]	
INCOMIN 2001	Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN)	Durelli 2002[194]	
Kappos 2011	Phase II, Multicenter, Randomized, Parallel-Group, Partially Blinded, Placebo and Avonex Controlled Dose Finding Study to Evaluate the Efficacy As Measured by Brain MRI Lesions, and Safety of 2 Dose Regimens of Ocrelizumab in Patients With RRMS	Kappos 2011[197]	
Knobler 1993	Systemic Recombinant Human Interferon-ß Treatment of Relapsing-Remitting Multiple Sclerosis: Pilot Study Analysis and Six-Year Follow-Up	Knobler 1993[209]	
Mokhber 2014	Cognitive dysfunction in patients with multiple sclerosis treated with different types of interferon beta: A randomized clinical trial	Mokhber 2014[184]	Mokhber 2015[185] (HRQoL)
MSCRG 1996	Intramuscular Interferon Beta-la for Disease Progression in Relapsing Multiple Sclerosis	Jacobs 1996[198]	Fischer 2000,[201] Goodkin 1998,[200] Granger 2003,[202] Miller 2011,[203] Rudick 1997[199]
NASG 2004	Interferon beta-1b in secondary progressive MS	Panitch 2004[221]	
Pakdaman 2007	Effect of early interferon beta-1a therapy on conversion to multiple sclerosis in Iranian patients with a first demyelinating event	Pakdaman 2007[171]	
PreCISe 2009	A Multinational, Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel Group Study to Evaluate the Effect of Early Glatiramer Acetate Treatment in Delaying the Conversion to Clinically Definite Multiple Sclerosis (CDMS) of Subjects Presenting With Clinically Isolated Syndrome (CIS)	Comi 2009[172]	

PRISMS 1998	Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis	PRISMS Study Group 1998[187]	Patten 2001[206] (depression), Gold 2005[281] (4 year safety and tolerability)
REFLEX 2012	A Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter Clinical Trial of Rebif New Formulation (44 Microgram [Mcg] Three Times Weekly [Tiw] and 44 Mcg Once Weekly [ow]) in Subjects at High Risk of Converting to Multiple Sclerosis (REFLEX)	Comi 2012[173]	Freedman 2014[176] (Subgroup analysis), CADTH 2013[282]
REFORMS 2012	A Randomized, Multicenter, Two Arm, Open Label, Twelve Week Phase IIIb Study to Evaluate the Tolerability of Rebif (New Formulation) (IFN Beta-1a) and Betaseron (IFN Beta-1b) in IFN-naive Subjects With Relapsing Remitting Multiple Sclerosis (RRMS) Followed by a Single Arm, Eighty-two Week Minimum, Rebif (New Formulation) Only Safety Extension	Singer 2012[195]	
REGARD 2008	Phase IV, Multicenter, Open Label, Randomized Study of Rebif® 44 mcg Administered Three Times Per Week by Subcutaneous Injection Compared With Copaxone® 20 mg Administered Daily by Subcutaneous Injection in the Treatment of Relapsing Remitting Multiple Sclerosis	Mikol 2008[190]	
REMAIN 2012	Phase IV, Multicenter, Open Label, Randomized Study of Rebif® 44mcg Administered Three Times Per Week by Subcutaneous Injection Compared With no Treatment in the Therapy of Relapsing Multiple Sclerosis After Mitoxantrone	Rieckmann 2012[181]	
Schwartz 1997	The Quality-of-Life Effects of Interferon Beta-1b in Multiple Sclerosis	Schwartz 1997[179]	
SPECTRIMS 2001	Randomized controlled trial of interferon beta-1a in secondary progressive MS	SPECTRIMS Study Group 2001[222]	

23 Appendix 5: Overview of systematic reviews in RRMS, SPMS and CIS: methods and results

23.1 *Objective*

To provide an overview of systematic reviews, published in the last five years, of studies that assessed the cost-effectiveness of treating relapsing remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS) and/or clinically isolated syndrome (CIS).

Search strategy. The following electronic databases were searched from January 2011 to January 2016: MEDLINE (Ovid); MEDLINE In-Process Citations and Daily Update (Ovid); Embase (Ovid); Cochrane Library (Wiley), including NHS EED, and HTA databases; Science Citation Index (Web of Knowledge), Research Papers in Economics (RePEC) and the Cost-effectiveness Analysis (CEA) Registry. The database searches were kept broad, with search terms for MS and CIS combined with economic / HRQoL terms and systematic reviews terms (based on recognised search filters [224-227] where appropriate. Searches for MS and CIS were performed separately, but results were deduplicated and then combined for assessment. A full record of searches is provided at the end of this appendix. The searches were limited to reviews published in or after 2011. All bibliographic records identified through the electronic searches were collected in a managed reference database. The reference lists of included studies were also checked. Grey literature searches was undertaken using the online resources of various regulatory bodies, health service research agencies, professional societies and patient organisations.

Based on the quality assessment of these reviews, we considered six studies[230, 232-236] to be methodological robust and likely to capture economic analyses pre 2012. Hence, we have undertaken a search of primary studies (relapsisng remitting multiple sclerosis) with a search limited to 2012 and later.

Study selection. Selection of studies was undertaken by PA and checked by HM using the following defined criteria.

Inclusion criteria. Systematic reviews of economic evaluations that involve the use of economic models in RRMS/SPMS/CIS were included. Systematic reviews of health-related quality of life (HRQoL) studies in RRMS/SPMS/CIS were also be selected at this stage for later review.

Quality appraisal. The studies were appraised against A Measurement Tool to Assess Systematic Reviews (AMSTAR) framework for best practice in undertaking systematic reviews. AMSTAR assessment tool consists of series of criteria/questions (e.g. a priori design, study selection and data extraction, comprehensive literature search or methods used to combine the findings) to check whether these have been satisfactorily reported. Appraisal of the methodological quality of these studies was undertaken by two reviewers (HM and PA). Studies quality assessed by one reviewer was cross-checked by the other. Any disagreements were resolved by discussion or by recourse to a third-party reviewer (JM).

Results. The electronic database searches identified 1566 records (Figure 36). After removing duplicates, 1023 records were screened for inclusion. On the basis of title and abstract, 966 records were excluded and the remaining 57 records were included for full-text screening. A further 48 articles were excluded at the full-text

stage, leaving nine systematic reviews[230-238]. Nine systematic reviews included eight economic evaluation studies[230-237] and one systematic review[238] on studies that used a generic tool to measure HRQoL for people with multiple sclerosis.

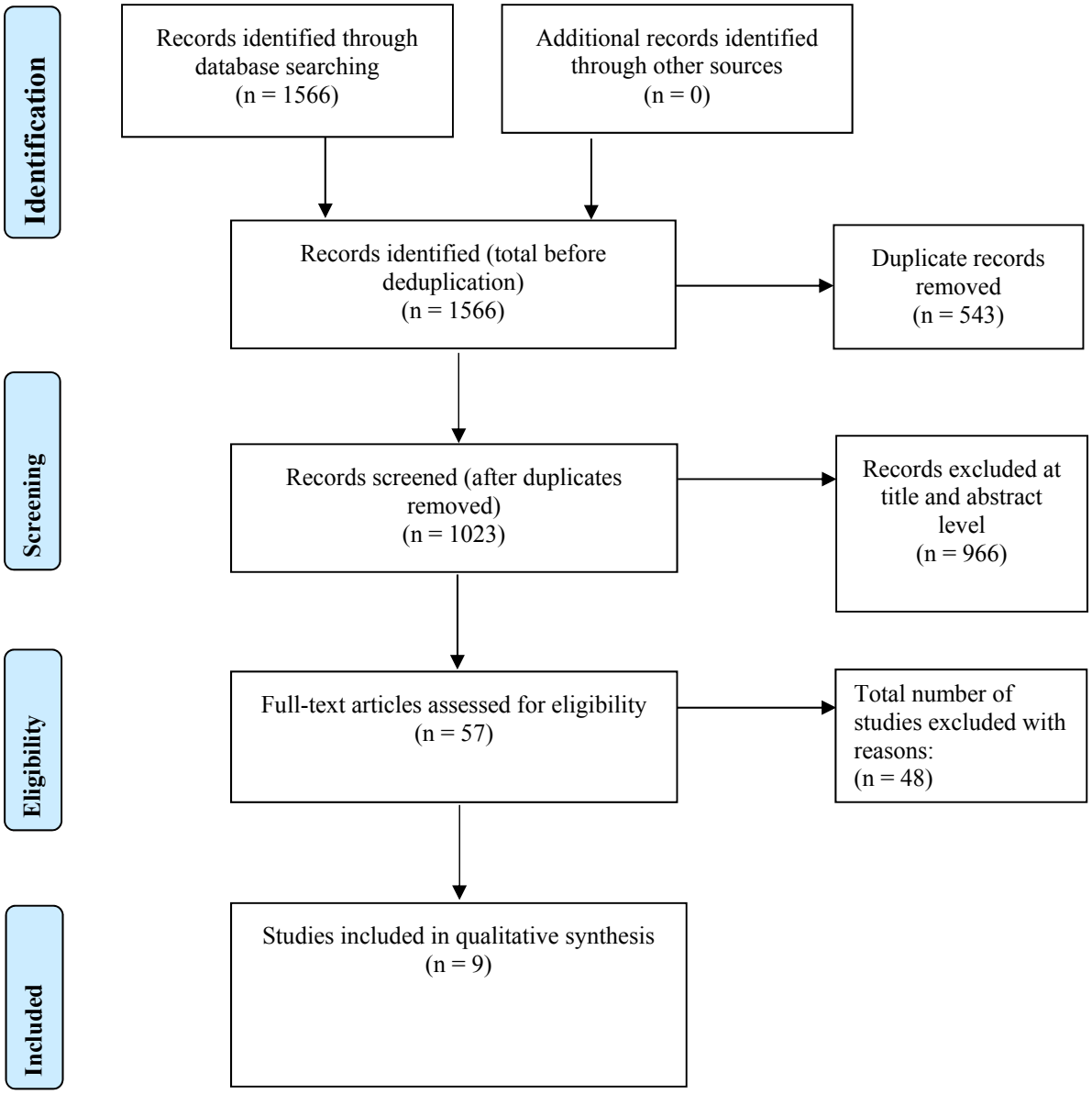

Figure 36: PRISMA flowchart, review of systematic reviews of economic evaluations

23.2 *Summary*

We have identified nine[230-238] systematic reviews published since January 2011, which included eight[230-237] reviews on economic evaluation studies and one[238] review which looked at generic tools used to measure health-related quality of life in people with multiple sclerosis.

We appraised these studies against the AMSTAR methodological assessment tool. Details on how each review performed can be found in Table 90. Based on our appraisal, systematic reviews generally performed satisfactorily in terms of stating an 'a prori' design of the review, stating the characteristics of all included studies, and stating the status of the publication. Though helpful, these reviews were subjected to some limitations. First, it was unclear in most studies if authors undertook study selection and data extraction in duplicate. Second, while some studies[230, 232, 236] provided a list of included studies, some authors[231, 233-235, 237, 238] have not provided a list of excluded studies. Third, it as unclear or not stated if authors assessed and/or documented the scientific quality of the included studies.

23.3 *Full record of searches*

23.3.1 MS searches

Medline (Ovid), searched 26/01/2016

Exact database: Ovid MEDLINE(R) 1946 to January Week 2 2016

1	exp Multiple Sclerosis/	46764
2	multiple sclerosis.tw.	49799
3	1 or 2	57188
4	exp Economics/	517314
5	exp "Costs and Cost Analysis"/	193082
6	Health Status/	63909
7	exp "Quality of Life"/	131614
8	exp Quality-Adjusted Life Years/	7896
9	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	475628
10	(health state* or health status).tw.	41055
11	(qaly* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or HUI).tw.	140813
12	(markov or time trade off or TTO or standard gamble or hrql or hrqol or disabilit* or disutilit*).tw.	133533
13	(quality adj2 life).tw.	154937
14	(decision adj2 model).tw.	4073
15	(visual analog* scale* or discrete choice experiment* or health* year* equivalen* or (willing* adj2 pay)).tw.	33173
16	("resource use" or resource utili?ation).tw.	9570
17	(well-being or wellbeing).tw.	46483

18	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	1328233
19	3 and 18	9165
20	(metaanalys* or meta analys* or meta-analys*).tw.	69140
21	(systematic* and review*).mp.	94951
22	meta analysis.pt.	60117
23	(literature and review*).mp.	315101
24	(review* adj10 (model* or cost* or economic* or "quality of life" or HRQoL or HRQL or utilit*)).tw.	37856
25	20 or 21 or 22 or 23 or 24	452492
26	19 and 25	551
27	limit 19 to systematic reviews	409
28	26 or 27	698
29	limit 28 to yr="2011 -Current"	305

Medline In-Process & Other Non-Indexed Citations (Ovid), searched 26/01/2016

Exact database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 25, 2016

1	multiple sclerosis.tw.	4878
2	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	69030
3	(health state* or health status).tw.	4219
4	(qaly* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or HUI).tw.	19706
5	(markov or time trade off or TTO or standard gamble or hrql or hrqol or disabilit* or disutilit*).tw.	16928
6	(quality adj2 life).tw.	22185
7	(decision adj2 model).tw.	500
8	(visual analog* scale* or discrete choice experiment* or health* year* equivalen* or (willing* adj2 pay)).tw.	5276
9	("resource use" or resource utili?ation).tw.	1372
10	(well-being or wellbeing).tw.	6440
11	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	126738
12	1 and 11	1295
13	(metaanalys* or meta analys* or meta-analys*).tw.	14035
14	(systematic* and review*).tw.	18717
15	(literature and review*).tw.	40052
16	(review* adj10 (model* or cost* or economic* or "quality of life" or HRQoL or HRQL or utilit*)).tw.	6244
17	13 or 14 or 15 or 16	62995
18	12 and 17	93
19	limit 12 to systematic reviews	63
20	18 or 19	105

21	limit 20 to yr="2011 -Current"	91

Embase (Ovid), searched 26/01/2016

Exact database: Embase 1974 to 2016 Week 04

1	multiple sclerosis/	93609
2	multiple sclerosis.tw.	80240
3	1 or 2	101212
4	exp health economics/	677659
5	exp health status/	164988
6	exp "quality of life"/	325811
7	exp quality adjusted life year/	15391
8	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	713057
9	(health state* or health status).tw.	57400
10	(qaly* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF6D or SF-6D or HUI).tw.	223035
11	(markov or time trade off or TTO or standard gamble or hrql or hrqol or disabilit* or disutilit*).tw.	208655
12	(quality adj2 life).tw.	270996
13	(decision adj2 model).tw.	6739
14	(visual analog* scale* or discrete choice experiment* or health* year* equivalen*).tw.	49099
15	("resource use" or resource utili?ation).tw.	17555
16	(well-being or wellbeing or (willing* adj2 pay)).tw.	74545
17	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	1972705
18	3 and 17	20936
19	meta analysis/	103317
20	(metaanalys* or meta analys* or meta-analys*).tw.	110582
21	"systematic review"/	100520
22	(systematic* adj3 review*).tw.	103537
23	(literature adj3 review*).tw.	245646
24	(review* adj10 (model* or cost* or economic* or "quality of life" or HRQoL or HRQL or utilit*)).tw.	56320
25	19 or 20 or 21 or 22 or 23 or 24	486435
26	18 and 25	994
27	limit 18 to "systematic review"	312
28	26 or 27	994
29	limit 28 to yr="2011 -Current"	566

DARE (Cochrane Library), searched 13/01/2016

ID	Search	Hits

#1	MeSH descriptor: [Multiple Sclerosis] explode all trees	1916
#2	multiple sclerosis:ti,ab,kw	4938
#3	#1 or #2	4942
#4	MeSH descriptor: [Economics] explode all trees	25789
#5	MeSH descriptor: [Costs and Cost Analysis] explode all trees	23940
#6	MeSH descriptor: [Health Status] explode all trees	5540
#7	MeSH descriptor: [Quality of Life] explode all trees	15431
#8	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees	3942
#9	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*):ti,ab,kw	51646
#10	(health next (state* or status)):ti,ab,kw	7475
#11	(qaly* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or HUI):ti,ab,kw	12645
#12	(markov or "time trade off" or TTO or "standard gamble" or hrql or hrqol or disabilit* or disutilit*):ti,ab,kw	18569
#13	(quality near/2 life):ti,ab,kw	42732
#14	(decision near/2 model):ti,ab,kw	393
#15	((visual next analog* next scale*) or ("discrete choice" next experiment*) or (health* next year* next equivalen*) or (willing* near/2 pay)):ti,ab,kw	19706
#16	("resource use" or resource next utili?ation):ti,ab,kw	1571
#17	(well-being or wellbeing):ti,ab,kw	5981
#18	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17	125705
#19	#3 and #18 Publication Year from 2011 to 2016	1048

Total all databases: 1048

Other Reviews (DARE): 11

HTA (CRD), searched 13/01/2016

Any field: multiple sclerosis
AND
Publication year 2011 to 2016
AND
HTA selected

Total: 38

NHS EED (Cochrane Library), searched 13/01/2016

n.b. Since March 2015, NHS EED is no longer updated

ID	Search	Hits
#1	MeSH descriptor: [Multiple Sclerosis] explode all trees	1916
#2	multiple sclerosis:ti,ab,kw	4938
#3	#1 or #2	4942
#4	(metaanalys* or (meta next analys*) or meta-analys*):ti,ab,kw	26655
#5	review* or literature or systematic*:ti,ab,kw	112066
#6	#4 or #5	114328
#7	#3 and #6 Publication Year from 2011 to 2016	282

All databases: 282

Economic Evaluations (NHS EED): 31

Science Citation Index (Web of Knowledge), searched 26/01/2016

# 8	394	#7 AND #2 AND #1 *Indexes=SCI-EXPANDED Timespan=2011-2016*
# 7	232,254	#6 OR #5 OR #4 OR #3 *Indexes=SCI-EXPANDED Timespan=2011-2016*
# 6	24,398	TS=(review* NEAR/10 (model* or cost* or economic* or "quality of life" or HRQoL or HRQL or utilit*)) *Indexes=SCI-EXPANDED Timespan=2011-2016*
# 5	99,993	TS=(literature AND review*) *Indexes=SCI-EXPANDED Timespan=2011-2016*
# 4	60,945	TS=(systematic* AND review*) *Indexes=SCI-EXPANDED Timespan=2011-2016*
# 3	102,963	TS=(metaanalys* or (meta NEAR/1 analys*)) *Indexes=SCI-EXPANDED Timespan=2011-2016*
# 2	573,437	TS=("quality of life" or QoL or hrql or hrqol or ("quality adjusted life" NEAR/1 year*) or QALY* or cost* or economic* or pharmacoeconomic* or pharmaco-economic* or euro-qol or utilit* or disutilit* or euroqol or "euro qol" or EQ5D or EQ-5D or SF-36 or SF36 or SF-6D or SF6D or HUI or (time NEAR/1 trade*) or TTO or "standard gamble" or markov or (decision NEAR/2 model*) or (visual NEAR/1 analog*) or "discrete choice" or ((health* NEAR/1 year*) NEAR/1 equivalen*) or (health NEAR/1 stat*) or "willingness to pay" or "resource use" or (resource NEAR/1 utili?ation) or wellbeing or well-being) *Indexes=SCI-EXPANDED Timespan=2011-2016*
# 1	29,661	TS="multiple sclerosis" *Indexes=SCI-EXPANDED Timespan=2011-2016*

RePEc, searched 13/01/2016

EconPapers

Free text: "multiple sclerosis"

125

Sorted by item date

Total number published from 2011 to 2016: 36

CEA Registry, searched 13/01/2016

Contained details of articles up to 2013 at time of search

Basic Search

Articles

Full Search Contents: multiple sclerosis

Total number published from 2011 to 2016: 14

ScHARR HUD, searched 13/01/2016

multiple sclerosis in any field

AND

2011 to 2016 in Year Published

Total: 9

23.3.2 CIS searches

Medline (Ovid), searched 10/02/2016

Exact database: Ovid MEDLINE(R) 1946 to January Week 4 2016

1	Demyelinating Diseases/	10446
2	Myelitis, Transverse/	1153
3	exp Optic Neuritis/	6737
4	Encephalomyelitis, Acute Disseminated/	1689
5	Demyelinating Autoimmune Diseases, CNS/	316
6	demyelinating disease*.tw.	4725
7	transverse myelitis.tw.	1356
8	neuromyelitis optica.tw.	1735
9	optic neuritis.tw.	3792
10	acute disseminated encephalomyelitis.tw.	1098
11	devic.tw.	107
12	ADEM.tw.	574
13	demyelinating disorder.tw.	335
14	clinically isolated syndrome.tw.	644
15	first demyelinating event.tw.	68
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	24564
17	exp Economics/	517857
18	exp "Costs and Cost Analysis"/	193384
19	Health Status/	64061
20	exp "Quality of Life"/	131967
21	exp Quality-Adjusted Life Years/	7948
22	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	476878
23	(health state* or health status).tw.	41167
24	(qaly* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or HUI).tw.	141292
25	(markov or time trade off or TTO or standard gamble or hrql or hrqol or disabilit* or disutilit*).tw.	133897
26	(quality adj2 life).tw.	155431
27	(decision adj2 model).tw.	4092
28	(visual analog* scale* or discrete choice experiment* or health* year* equivalen* or (willing* adj2 pay)).tw.	33282
29	("resource use" or resource utili?ation).tw.	9601
30	(well-being or wellbeing).tw.	46641
31	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	1331084
32	(metaanalys* or meta analys* or meta-analys*).tw.	69583
33	(systematic* and review*).mp.	95472
34	meta analysis.pt.	60490

35	(literature and review*).mp.	315829
36	(review* adj10 (model* or cost* or economic* or "quality of life" or HRQoL or HRQL or utilit*)).tw.	37973
37	32 or 33 or 34 or 35 or 36	453843
38	16 and 31	1437
39	37 and 38	82
40	limit 38 to systematic reviews	51
41	39 or 40	107
42	limit 41 to yr="2011 -Current"	51

Total minus duplicates with MS cost SRs search: 11

Medline In-process, searched 11/02/2016

Exact database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations February 10, 2016

1	demyelinating disease*.tw.	406
2	transverse myelitis.tw.	148
3	neuromyelitis optica.tw.	322
4	optic neuritis.tw.	360
5	acute disseminated encephalomyelitis.tw.	128
6	devic.tw.	6
7	ADEM.tw.	84
8	demyelinating disorder.tw.	56
9	clinically isolated syndrome.tw.	118
10	first demyelinating event.tw.	6
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	1259
12	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	69098
13	(health state* or health status).tw.	4217
14	(qaly* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or HUI).tw.	19723
15	(markov or time trade off or TTO or standard gamble or hrql or hrqol or disabilit* or disutilit*).tw.	16916
16	(quality adj2 life).tw.	22287
17	(decision adj2 model).tw.	492
18	(visual analog* scale* or discrete choice experiment* or health* year* equivalen* or (willing* adj2 pay)).tw.	5321
19	("resource use" or resource utili?ation).tw.	1372
20	(well-being or wellbeing).tw.	6423
21	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	126925
22	(metaanalys* or meta analys* or meta-analys*).tw.	13978
23	(systematic* and review*).tw.	18746
24	(literature and review*).tw.	40310

25	(review* adj10 (model* or cost* or economic* or "quality of life" or HRQoL or HRQL or utilit*)).tw.	6282
26	22 or 23 or 24 or 25	63191
27	11 and 21	186
28	limit 27 to systematic reviews	7
29	26 and 27	12
30	28 or 29	14
31	limit 30 to yr="2011 -Current"	11

Total minus duplicates with MS cost SRs search: 5

Embase (Ovid), searched 11/02/2016

Exact database: Embase 1974 to 2016 Week 06

1	demyelinating disease/	12216
2	myelitis/	6771
3	optic neuritis/	6979
4	acute disseminated encephalomyelitis/	1378
5	myelooptic neuropathy/	4897
6	demyelinating disease*.tw.	7443
7	transverse myelitis.tw.	2462
8	neuromyelitis optica.tw.	4162
9	optic neuritis.tw.	6551
10	acute disseminated encephalomyelitis.tw.	1762
11	devic.tw.	229
12	ADEM.tw.	1211
13	demyelinating disorder.tw.	624
14	clinically isolated syndrome.tw.	1758
15	first demyelinating event.tw.	159
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	34739
17	exp health economics/	679154
18	exp health status/	165534
19	exp "quality of life"/	327227
20	exp quality adjusted life year/	15498
21	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	715448
22	(health state* or health status).tw.	57542
23	(qaly* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF6D or SF-6D or HUI).tw.	223904
24	(markov or time trade off or TTO or standard gamble or hrql or hrqol or disabilit* or disutilit*).tw.	209301
25	(quality adj2 life).tw.	272302

26	(decision adj2 model).tw.	6788
27	(visual analog* scale* or discrete choice experiment* or health* year* equivalen*).tw.	49341
28	("resource use" or resource utili?ation).tw.	17623
29	(well-being or wellbeing or (willing* adj2 pay)).tw.	74888
30	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29	1979047
31	meta analysis/	103826
32	(metaanalys* or meta analys* or meta-analys*).tw.	111288
33	"systematic review"/	101172
34	(systematic* adj3 review*).tw.	104294
35	(literature adj3 review*).tw.	246476
36	(review* adj10 (model* or cost* or economic* or "quality of life" or HRQoL or HRQL or utilit*)).tw.	56523
37	31 or 32 or 33 or 34 or 35 or 36	488476
38	16 and 30	3989
39	37 and 38	212
40	limit 38 to "systematic review"	64
41	39 or 40	212
42	limit 41 to yr="2011 -Current"	113

Total minus duplicates with MS cost SRs search: 47

DARE (Cochrane Library), searched 13/01/2016

#1	MeSH descriptor: [Demyelinating Diseases] this term only	71
#2	MeSH descriptor: [Myelitis, Transverse] this term only	6
#3	MeSH descriptor: [Optic Neuritis] explode all trees	95
#4	MeSH descriptor: [Encephalomyelitis, Acute Disseminated] this term only	3
#5	MeSH descriptor: [Demyelinating Autoimmune Diseases, CNS] this term only	2
#6	demyelinating next disease*:ti,ab,kw (Word variations have been searched)	186
#7	transverse myelitis:ti,ab,kw (Word variations have been searched)	14
#8	neuromyelitis optica:ti,ab,kw (Word variations have been searched)	20
#9	optic neuritis:ti,ab,kw (Word variations have been searched)	220
#10	acute disseminated encephalomyelitis:ti,ab,kw (Word variations have been searched)	13
#11	devic:ti,ab,kw (Word variations have been searched)	2
#12	ADEM:ti,ab,kw (Word variations have been searched)	4
#13	demyelinating disorder:ti,ab,kw (Word variations have been searched)	49
#14	clinically isolated syndrome:ti,ab,kw (Word variations have been searched)	114
#15	first demyelinating event:ti,ab,kw (Word variations have been searched)	72
#16	single demyelinating event:ti,ab,kw (Word variations have been searched)	9
#17	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16	561
#18	MeSH descriptor: [Economics] explode all trees	26697
#19	MeSH descriptor: [Costs and Cost Analysis] explode all trees	24728
#20	MeSH descriptor: [Health Status] explode all trees	6149
#21	MeSH descriptor: [Quality of Life] explode all trees	17692
#22	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees	4063
#23	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*):ti,ab,kw	53199
#24	(health next (state* or status)):ti,ab,kw	7906

#25	(qaly* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or HUI):ti,ab,kw	13317
#26	(markov or "time trade off" or TTO or "standard gamble" or hrql or hrqol or disabilit* or disutilit*):ti,ab,kw	19514
#27	(quality near/2 life):ti,ab,kw	44945
#28	(decision near/2 model):ti,ab,kw	418
#29	((visual next analog* next scale*) or ("discrete choice" next experiment*) or (health* next year* next equivalen*) or (willing* near/2 pay)):ti,ab,kw	20672
#30	("resource use" or resource next utili?ation):ti,ab,kw	1657
#31	(well-being or wellbeing):ti,ab,kw	6305
#32	#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31	130941
#33	#17 and #32 Publication Year from 2011 to 2016	97

Total all databases: 97

Other Reviews (DARE): 0

NHS EED and HTA database (Cochrane Library), searched 11/02/2016

#1	MeSH descriptor: [Demyelinating Diseases] this term only	71
#2	MeSH descriptor: [Myelitis, Transverse] this term only	6
#3	MeSH descriptor: [Optic Neuritis] explode all trees	95
#4	MeSH descriptor: [Encephalomyelitis, Acute Disseminated] this term only	3
#5	MeSH descriptor: [Demyelinating Autoimmune Diseases, CNS] this term only	2
#6	demyelinating next disease*:ti,ab,kw (Word variations have been searched)	186
#7	transverse myelitis:ti,ab,kw (Word variations have been searched)	14
#8	neuromyelitis optica:ti,ab,kw (Word variations have been searched)	20
#9	optic neuritis:ti,ab,kw (Word variations have been searched)	220
#10	acute disseminated encephalomyelitis:ti,ab,kw (Word variations have been searched)	13
#11	devic:ti,ab,kw (Word variations have been searched)	2
#12	ADEM:ti,ab,kw (Word variations have been searched)	4
#13	demyelinating disorder:ti,ab,kw (Word variations have been searched)	49
#14	clinically isolated syndrome:ti,ab,kw (Word variations have been searched)	114
#15	first demyelinating event:ti,ab,kw (Word variations have been searched)	72
#16	single demyelinating event:ti,ab,kw (Word variations have been searched)	9
#17	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 Publication Year from 2011 to 2016	241

Total all databases: 241

Technology Assessments (HTA database): 1

Economic Evaluations (NHS EED): 2

Science Citation Index (Web of Knowledge), searched 24/02/2016

# 18	41	#17 *Indexes=SCI-EXPANDED Timespan=2011-2016*
# 17	59	#16 AND #11 AND #10 *Indexes=SCI-EXPANDED Timespan=All years*
# 16	497,345	#15 OR #14 OR #13 OR #12 *Indexes=SCI-EXPANDED Timespan=All years*

# 15	62,256	TS=(review* NEAR/10 (model* or cost* or economic* or "quality of life" or HRQoL or HRQL or utilit*)) *Indexes=SCI-EXPANDED Timespan=All years*
# 14	253,207	TS=(literature AND review*) *Indexes=SCI-EXPANDED Timespan=All years*
# 13	104,464	TS=(systematic* AND review*) *Indexes=SCI-EXPANDED Timespan=All years*
# 12	168,986	TS=(metaanalys* or (meta NEAR/1 analys*)) *Indexes=SCI-EXPANDED Timespan=All years*
# 11	1,495,884	TS=("quality of life" or QoL or hrql or hrqol or ("quality adjusted life" NEAR/1 year*) or QALY* or cost* or economic* or pharmacoeconomic* or pharmaco-economic* or euro-qol or utilit* or disutilit* or euroqol or "euro qol" or EQ5D or EQ-5D or SF-36 or SF36 or SF-6D or SF6D or HUI or (time NEAR/1 trade*) or TTO or "standard gamble" or markov or (decision NEAR/2 model*) or (visual NEAR/1 analog*) or "discrete choice" or ((health* NEAR/1 year*) NEAR/1 equivalen*) or (health NEAR/1 stat*) or "willingness to pay" or "resource use" or (resource NEAR/1 utili?ation) or wellbeing or well-being) *Indexes=SCI-EXPANDED Timespan=All years*
# 10	16,921	#9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 9	96	TS="first demyelinating event" *Indexes=SCI-EXPANDED Timespan=All years*
# 8	1,202	TS="clinically isolated syndrome" *Indexes=SCI-EXPANDED Timespan=All years*
# 7	690	TS="ADEM" *Indexes=SCI-EXPANDED Timespan=All years*
# 6	464	TS="devic" *Indexes=SCI-EXPANDED Timespan=All years*
# 5	1,605	TS=("acute disseminated" NEAR/1 encephalomyelitis) *Indexes=SCI-EXPANDED Timespan=All years*
# 4	3,547	TS="neuromyelitis optica" *Indexes=SCI-EXPANDED Timespan=All years*
# 3	4,593	TS="optic neuritis" *Indexes=SCI-EXPANDED Timespan=All years*
# 2	1,703	TS=(transverse NEAR/1 myelitis) *Indexes=SCI-EXPANDED Timespan=All years*
# 1	6,814	TS=(demyelinating NEAR/2 (disease* OR disorder*)) *Indexes=SCI-EXPANDED Timespan=All years*

Total minus duplicates with MS cost SRs search: 4

<u>RePEc, searched 24/02/2016</u>

EconPapers first search

Free text: demyelinating OR myelitis OR "neuromyelitis optica" OR "optic neuritis" OR "acute disseminated encephalomyelitis" OR "clinically isolated syndrome"

2

Sorted by item date

Total number published from 2011 to 2016: 1

EconPapers second search

Keywords and Title: devic OR ADEM

0

Total: 1

Total minus duplicates with MS cost SRs search: 1

CEA Registry, searched 24/02/2016

Contains details of articles up to 2013

Basic Search

Articles

Full Search Contents: demyelinating: 3

Full Search Contents: myelitis: 1

Full Search Contents: neuromyelitis optica: 0

Full Search Contents: optic neuritis: 0

Full Search Contents: encephalomyelitis: 0

Full Search Contents: clinically isolated syndrome: 2

Total: 6

Total number published from 2011 to 2016: 1

Total minus duplicates with MS cost SRs search: 0

ScHARR HUD, searched 24/02/2016

demyelinating in any field: 0

myelitis in any field: 0

neuromyelitis optica in any field: 0

optic neuritis in any field: 0

acute disseminated encephalomyelitis in any field: 0

clinically isolated syndrome in any field: 0

Total: 0

23.3.3 Grey literature

Searches of websites were undertaken concurrently for both clinical effectiveness and cost-effectiveness. For a record of these searches, see Appendix 1.

Table 90: Quality assessment of systematic reviews of economic evaluations

Criteria	Study								
	Allen et al., 2015[230]	Castrop et al., 2013[231]	Guo et al., 2014[232]	Hawton et al., 2013[233]	Owens et al., 2013[234]	Thompson et al., 2013[235]	Yamamoto and Campbell 2012[236]	Zalesak et al., 2014[237]	Kuspinar et al., 2014[238]
Was an 'a priori' design provided?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was there duplicate study selection and data extraction?	N	U	Y	U	N	N	U	U	N
Was a comprehensive literature search performed?	Y Sensitive subject search used in multiple sources including NICE website, but UK terms added to database searches using .mp., which may be a concern because it reduced numbers considerably	N Just MEDLINE (PubMed) using just 2 broad MeSH terms – one for MS and one for 'costs and cost analysis' (assume exploded?). No free text or other searching. No specific terms for CIS	Y MEDLINE (PubMed) using just specific 'cost-benefit analysis' MeSH term with MS in all fields and generic and brand names for DMTs. References of included after Title/Abstract sift checked	Y Multiple sources searched. References of retrieved studies and existing review articles checked and citation searches undertaken	N Non-systematic search Just MEDLINE (PubMed) Unclear if MeSH heading Health Care Economics and Organizations was exploded, but some free text terms used. No other searching for	Y? MEDLINE (Ovid and PubMed) using just 2 exploded broad MeSH terms – one for MS and one for 'costs and cost analysis'. References of published (included?) studies checked	Y? MEDLINE (PubMed) using just specific 'cost-benefit analysis' with 'the general search term' MS (assume free text and MeSH?). Generic and brand names for DMTs incorporated - unclear how, but numbers in flowshart imply combined with AND.	U	Y Multiple databases searched using search strategy appropriate to the specific measures of interest, but no general HQoL terms used.

Criteria	Study								
	Allen et al., 2015[230]	Castrop et al., 2013[231]	Guo et al., 2014[232]	Hawton et al., 2013[233]	Owens et al., 2013[234]	Thompson et al., 2013[235]	Yamamoto and Campbell 2012[236]	Zalesak et al., 2014[237]	Kuspinar et al., 2014[238]
					results section undertaken		CEA Registry and NHS EED also searched		
Was the status of publication (i.e. grey literature) used as an inclusion criterion?	N	N	Y	Y	Y	Y	Y	Y	Y
Was a list of studies (included and excluded) provided?	Included – Y (18, relating to 12 models) Excluded – Y (8)	Included – Y (4) Excluded – N	Included – Y (12) Excluded – Y (13)	Included – Y (38) Excluded – N (20)	Included – Y (53 on cost, cost-effectiveness, productivity decline, or abstenteeism)	Included – Y (35) Excluded – N	Included – Y (22) Excluded – Y (28)	N	Included – Y (15) Excluded – N
Were the characteristics of the included studies provided?	Y	Y	Y	Y	Y	Y	Y	N	Y
Was the scientific quality of the included studies assessed and documented?	Y	Y	U	N	N	N	Y	N	Y
Was the scientific	Y	Y	U	NA	NA	NA	Y	NA	Y

Criteria	Study								
	Allen et al., 2015[230]	Castrop et al., 2013[231]	Guo et al., 2014[232]	Hawton et al., 2013[233]	Owens et al., 2013[234]	Thompson et al., 2013[235]	Yamamoto and Campbell 2012[236]	Zalesak et al., 2014[237]	Kuspinar et al., 2014[238]
quality of the included studies used appropriately in formulating conclusions?									
Were the methods used to combine the findings of studies appropriate?	NA	NA	NA	NA	NA	NA	NA	NA	Y
Was the likelihood of publication bias assessed?	NA	NA	NA	NA	NA	NA	NA	NA	Y
Was the conflict of interest stated?	Y	Y	Y	N	Y	Y	Y	Y	Y
Additional criteria used by the assessment group									
Search date	03/03/2014	14/12/2012	01/04/2013	12/2011	15/09/2011	26/04/2012	09/2012	Unclear	08/10/2013
Scope	RRMS, DMTs, UK, cost-effectiveness models	CIS, Interferon beta, comparative, cost and cost-effectiveness	MS, DMTs, cost-effectiveness models	MS, cost-effectiveness	MS, DMTs, cost and cost-effectiveness	MS, DMTs, cost-effectiveness models	MS, DMTs, cost-effectiveness	MS, Breast Cancer and Rheumatoid Arthritis, specialty medicines, market research and cost-effectiveness	MS, Specific generic utility measures (HUI, EQ-5D, SF-6D, Quality of Well-Being)

Criteria	Study								
	Allen et al., 2015[230]	Castrop et al., 2013[231]	Guo et al., 2014[232]	Hawton et al., 2013[233]	Owens et al., 2013[234]	Thompson et al., 2013[235]	Yamamoto and Campbell 2012[236]	Zalesak et al., 2014[237]	Kuspinar et al., 2014[238]
CIS, clinically isolated syndrome; DMT, disease modifying treatment; EQ-5D, eurqol five dimensions; HUI, health utility index; MS, multiple sclerosis; N-no; NA-not applicable; SF-6D, short form six dimensions; U-unclear; Y-yes;									

24 Appendix 6: Cost-effectiveness review of clinically isolated syndrome studies

24.1 *Full record of searches*

24.1.1 Main search

Medline (Ovid), searched 06/04/2016

Exact database: Ovid MEDLINE(R) 1946 to March Week 4 2016

1	Demyelinating Diseases/	10532
2	Myelitis, Transverse/	1165
3	exp Optic Neuritis/	6821
4	Encephalomyelitis, Acute Disseminated/	1696
5	Demyelinating Autoimmune Diseases, CNS/	323
6	demyelinating disease*.tw.	4779
7	transverse myelitis.tw.	1371
8	neuromyelitis optica.tw.	1786
9	optic neuritis.tw.	3828
10	acute disseminated encephalomyelitis.tw.	1109
11	devic.tw.	107
12	ADEM.tw.	583
13	demyelinating disorder.tw.	339
14	clinically isolated syndrome.tw.	660
15	first demyelinating event.tw.	69
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	24812
17	exp Economics/	522024
18	exp "Costs and Cost Analysis"/	195358
19	exp Quality-Adjusted Life Years/	8146
20	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	484557
21	(decision adj2 model).tw.	4186
22	("resource use" or resource utili?ation).tw.	9821
23	(qaly* or (generic adj2 (instrument* or measure*)) or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or Health Utilities Index or HUI or 15D or Assessment of Quality of Life or AQOL or Quality of Well-Being or QWB).tw.	27152
24	17 or 18 or 19 or 20 or 21 or 22 or 23	885600
25	16 and 24	195

Medline In-Process & Other Non-Indexed Citations (Ovid), searched 06/04/2016

Exact database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations April 05, 2016

1	demyelinating disease*.tw.	415
2	transverse myelitis.tw.	150
3	neuromyelitis optica.tw.	329
4	optic neuritis.tw.	380
5	acute disseminated encephalomyelitis.tw.	136
6	devic.tw.	6
7	ADEM.tw.	85
8	demyelinating disorder.tw.	58
9	clinically isolated syndrome.tw.	122
10	first demyelinating event.tw.	6
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	1298
12	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	71278
13	(decision adj2 model).tw.	511
14	("resource use" or resource utili?ation).tw.	1444
15	(qaly* or (generic adj2 (instrument* or measure*)) or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or Health Utilities Index or HUI or 15D or Assessment of Quality of Life or AQOL or Quality of Well-Being or QWB).tw.	3504
16	quality-adjusted life year*.tw.	949
17	12 or 13 or 14 or 15 or 16	74654
18	11 and 17	23

Embase (Ovid), searched 06/04/2016

Exact database: Embase 1974 to 2016 Week 14

1	demyelinating disease/	12351
2	myelitis/	6889
3	optic neuritis/	7109
4	acute disseminated encephalomyelitis/	1437
5	myelooptic neuropathy/	4987
6	demyelinating disease*.tw.	7511
7	transverse myelitis.tw.	2498
8	neuromyelitis optica.tw.	4242
9	optic neuritis.tw.	6631
10	acute disseminated encephalomyelitis.tw.	1792
11	devic.tw.	231
12	ADEM.tw.	1224
13	demyelinating disorder.tw.	633
14	clinically isolated syndrome.tw.	1789
15	first demyelinating event.tw.	159
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	35248

17	multiple sclerosis/	94999
18	multiple sclerosis.tw.	81514
19	17 or 18	102763
20	exp *health economics/	212668
21	exp quality adjusted life year/	15786
22	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).ti.	164671
23	(decision adj2 model).tw.	6901
24	("resource use" or resource utili?ation).tw.	17938
25	(qaly* or (generic adj2 (instrument* or measure*)) or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or Health Utilities Index or HUI or 15D or Assessment of Quality of Life or AQOL or Quality of Well-Being or QWB).tw.	50631
26	20 or 21 or 22 or 23 or 24 or 25	371080
27	16 and 26	173

NHS EED and HTA database (Cochrane Library), searched 06/04/2016

ID	Search	Hits
#1	MeSH descriptor: [Demyelinating Diseases] this term only	71
#2	MeSH descriptor: [Myelitis, Transverse] this term only	6
#3	MeSH descriptor: [Optic Neuritis] explode all trees	95
#4	MeSH descriptor: [Encephalomyelitis, Acute Disseminated] this term only	3
#5	MeSH descriptor: [Demyelinating Autoimmune Diseases, CNS] this term only	2
#6	demyelinating next disease*:ti,ab,kw (Word variations have been searched)	187
#7	transverse myelitis:ti,ab,kw (Word variations have been searched)	14
#8	neuromyelitis optica:ti,ab,kw (Word variations have been searched)	20
#9	optic neuritis:ti,ab,kw (Word variations have been searched)	222
#10	acute disseminated encephalomyelitis:ti,ab,kw (Word variations have been searched)	13
#11	devic:ti,ab,kw (Word variations have been searched)	3
#12	ADEM:ti,ab,kw (Word variations have been searched)	4
#13	demyelinating disorder:ti,ab,kw (Word variations have been searched)	49
#14	clinically isolated syndrome:ti,ab,kw (Word variations have been searched)	116
#15	first demyelinating event:ti,ab,kw (Word variations have been searched)	72
#16	single demyelinating event:ti,ab,kw (Word variations have been searched)	9
#17	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16	566

Total all databases: 566

Technology Assessments: 2

Economic Evaluations: 3

Science Citation Index and Conference Proceedings – Science (Web of Knowledge), searched 06/04/2016

# 14	210	#13 AND #10 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 13	1,335,874	#11 or #12 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*

# 12	80,174	TS=((“quality adjusted life” NEAR/1 year*) or QALY* or (generic NEAR/2 (instrument* or measure*)) or euro-qol or euroqol or “euro qol” or EQ5D or EQ-5D or SF-36 or SF36 or SF-6D or SF6D or "health utilities index" or HUI or 15D or "assessment of quality of life" or AQOL or "Quality of Well-Being" or QWB or (decision NEAR/2 model*) or “resource use” or (resource NEAR/1 utili?ation)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 11	1,280,769	TS=(cost* or economic* or pharmacoeconomic* or pharmaco-economic*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 10	17,216	#9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 9	96	TS="first demyelinating event" *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 8	1,225	TS="clinically isolated syndrome" *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 7	711	TS="ADEM" *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 6	474	TS="devic" *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 5	1,620	TS=("acute disseminated" NEAR/1 encephalomyelitis) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 4	3,616	TS="neuromyelitis optica" *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 3	4,703	TS="optic neuritis" *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 2	1,732	TS=(transverse NEAR/1 myelitis) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 1	6,912	TS=(demyelinating NEAR/2 (disease* OR disorder*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*

RePEc, searched 06/04/2016

EconPapers first search

Free text: demyelinating OR myelitis OR "neuromyelitis optica" OR "optic neuritis" OR "acute disseminated encephalomyelitis" OR "clinically isolated syndrome"

2

EconPapers second search

Keywords and Title: devic OR ADEM

0

Total: 2

CEA Registry, searched 06/04/2016

Contains details of articles up to 2014 at time of search

Basic Search

Articles

Full Search Contents: demyelinating: 3

Full Search Contents: myelitis: 1

Full Search Contents: neuromyelitis optica: 0

Full Search Contents: optic neuritis: 0

Full Search Contents: encephalomyelitis: 0

Full Search Contents: clinically isolated syndrome: 2

Total: 6

ScHARR HUD, searched 06/04/2016

demyelinating in any field: 0

myelitis in any field: 0

neuromyelitis optica in any field: 0

optic neuritis in any field: 0

acute disseminated encephalomyelitis in any field: 0

clinically isolated syndrome in any field: 0

Total: 0

24.1.2 Additional search

CIS (or RRMS post 2011) registers or cohort natural history

Medline (Ovid), searched 16/06/2016

1	Demyelinating Diseases/
2	Myelitis, Transverse/
3	exp Optic Neuritis/
4	Encephalomyelitis, Acute Disseminated/
5	Demyelinating Autoimmune Diseases, CNS/
6	demyelinating disease*.tw.
7	transverse myelitis.tw.
8	neuromyelitis optica.tw.
9	optic neuritis.tw.

10	acute disseminated encephalomyelitis.tw.
11	devic.tw.
12	ADEM.tw.
13	demyelinating disorder.tw.
14	clinically isolated syndrome.tw.
15	first demyelinating event.tw.
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17	exp Registries/
18	(registry or registries).tw.
19	(register or registers).tw.
20	17 or 18 or 19
21	exp Cohort Studies/
22	(cohort adj (study or studies)).tw.
23	cohort analy$.tw.
24	(follow up adj (study or studies)).tw.
25	21 or 22 or 23 or 24
26	natural history.tw.
27	natural course.tw.
28	untreated.tw.
29	(("no" or "not") adj2 (treat* or therap*)).tw.
30	(natural adj2 (progression or development)).tw.
31	26 or 27 or 28 or 29 or 30
32	16 and 20
33	16 and 25 and 31
34	32 or 33
35	Multiple Sclerosis, Relapsing-Remitting/
36	relapsing remitting multiple sclerosis.tw.
37	35 or 36
38	limit 37 to yr="2011 -Current"
39	20 and 38
40	25 and 31 and 38
41	39 or 40
42	34 or 41

Table 91: Studies excluded from the cost-effectiveness review of CIS

	Reference	Reason for exclusion
1.	Casado V, Gubieras L, Romero-Pinel L, Matas E, Bau L, Lopez M*, et al.* Cost of the diagnosis of multiple sclerosis*. J Neurol*. 2009;256:S126.	Not full economic evaluation
2.	Fredrikson S, Prayoonwiwat N, Wicklein EM, Scherer P, Langdon D. Psychosocial aspects of clinically isolated syndrome (CIS) in Asia: Baseline data from the CogniCIS study Asian cohort*. J Neurol Sci*. 2009;285:S95.	Not an economic analysis
3.	Fredrikson S, Wicklein EM, Prayoonwiwat N, Beckmann K, Scherer P, Langdon D. Cognitive performance and health-related quality of life in clinically isolated syndrome (CIS) suggestive of multiple sclerosis: 2-year data from CogniCIS, a multinational, longitudinal study*. Eur J Neurol*. 2010;17:57.	Not an economic analysis
4.	Prayoonwiwat N, Nidhinandana S, Chankrachang S, Asawavichienjinda T, Tantirittisak T, Fredrikson S*, et al.* Psychosocial aspects of clinically isolated syndrome (CIS) in Asia: Baseline data from the cognicis study asian cohort*. Mult Scler*. 2010;16 (2):266-7.	Not an economic analysis
5.	Sanchez-Solino O, Grau C, Parra JC, Arroyo E. Quality of life in patients with high-risk clinically isolated syndrome treated with Avonex: Interim results of the AREMIN study*. J Neurol*. 2010;257:S190.	Not an economic analysis
6.	Stourac P, Horakova D, Tyblova M, Klimova E, Szilasiova J, Fenclova I*, et al.* Interim analysis of AMETYST: A phase 4 observational study of the impact of intramuscular interferon b-1a on quality of life, disability, and cognition in patients with clinically isolated syndrome/clinically definite multiple sclerosis*. Mult Scler*. 2012;1):486.	No model included
7.	Vermersch P, de Seze J, Delisse B, Lamaire S, Stojkovic T. Quality of life in multiple sclerosis: influence of interferon-beta 1a (Avonex (R)) treatment*. Mult Scler*. 2002;8(5):377-81.	Not an economic analysis

24.2 *Blank data extraction form for cost-effectiveness studies (clinically isolated syndrome)*

Date:
Study ID:
Name of first reviewer:
Name of second reviewer:

Study details	
Study title	
First author	
Co-authors	
Source of publication Journal yy;vol(issue):pp	
Language	
Publication type	
Inclusion criteria/study eligibility/PICOS	
Population	
Intervention(s)	
Comparator(s)	
Outcome(s)	
Study design	
Methods	
Setting and location	
Study perspective	
Comparators	
Time horizon	
Discount rate	
Outcomes	
Measurement of effectiveness	
Measurement and valuation of preference based outcomes	
Resource use and costs	
Currency, price date and conversion	
Model type	
Assumptions	
Analytical methods	
Results	
Study parameters	
Incremental costs and outcomes	
Characterising uncertainty	
Study findings	
Limitations	
Generalisability	
Source of funding	
Conflicts of interest	
Comments	
Authors conclusion	
Reviewer's conclusion	

24.3 *Quality assessment of economic evaluations in clinically isolated syndrome*

Table 92: CHEERS quality assessment for economic evaluations in CIS

Assessment	Studies								
	Fredrikson et al., 2013[239]	Iskedjian et al., 2005[242]	Lazzaro et al., 2009[241]	Kobelt et al., 2007[240]	Arbizu et al, 2009[243]	Caloyeras et al., 2009[245]	Caloyeras et al., 2008[244]	Caloyeras et al., 2012[246]	Zarco et al., 2014[247]
Title	Y	Y	Y	Y	Y	Y	Y	Y	Y
Abstract	Y	Y	Y	Y	Y	Y	Y	N	Y
Introduction									
Background and objectives	Y	Y	Y	N	Y	Y	Y	Y	Y
Methods									
Target population and subgroups	Y	Y	Y	Y	Y	Y	Y	Y	Y
Setting and location	N	N	N	N	Y	Y	Y	Y	Y
Study perspective	Y	Y	Y	Y	Y	Y	Y	Y	Y
Comparators	Y	Y	Y	Y	Y	Y	Y	Y	Y
Time horizon	Y	Y	Y	Y	Y	Y	Y	Y	Y
Discount rate	Y	Y	Y	Y	Y	Y	Y	Y	Y
Choice of health outcomes	Y	Y	Y	Y	Y	Y	Y	Y	Y
Measurement of effectiveness	Y	Y	Y	Y	UNC	UNC	Y	Y	Y
Measurement and valuation of preference-based outcomes	N	N	N	N	UNC	UNC	Y	Y	N/A
Estimating resources and costs	Y	Y	Y	N	Y	Y	Y	Y	Y
Currency, price date, and conversion	Y	Y	Y	Y	Y	Y	Y	Y	Y
Choice of model	Y	Y	Y	Y	UNC	UNC	UNC	Y	Y
Assumptions	Y	Y	Y	N	UNC	UNC	Y	Y	UNC
Analytical methods	Y	Y	Y	Y	Y	Y	Y	N	Y
Study parameters (results)	Y	Y	Y	Y	UNC	UNC	Y	N	Y
Incremental costs and outcomes	Y	Y	Y	Y	UNC	UNC	Y	Y	Y
Characterising uncertainty	Y	Y	Y	Y	UNC	UNC	UNC	N	Y
Study findings (discussion)	Y	Y	Y	Y	Y	Y	Y	Y	Y
Limitations	Y	Y	Y	N	UNC	UNC	UNC	Y	Y

Assessment	Studies								
	Fredrikson et al., 2013[239]	Iskedjian et al., 2005[242]	Lazzaro et al., 2009[241]	Kobelt et al., 2007[240]	Arbizu et al, 2009[243]	Caloyeras et al., 2009[245]	Caloyeras et al., 2008[244]	Caloyeras et al., 2012[246]	Zarco et al., 2014[247]
Generalizability	Y	Y	Y	UNC	UNC	UNC	UNC	Y	Y
Other									
Source of funding (other)	Y	Y	Y	N	UNC	UNC	UNC	Y	N
Conflicts of interest	Y	Y	Y	N	UNC	UNC	UNC	Y	N
N, no; N/A, not applicable; Y, yes; UNC-unclear									

Table 93: Philips' quality assessment for studies including an economic model in CIS

Philips' criteria		Studies								
		Fredrikson et al., 2013[239]	Iskedjian et al., 2005[242]	Lazzaro et al., 2009[241]	Kobelt et al., 2007[240]	Arbizu et al., 2009[243]	Caloyeras et al., 2008[244]	Caloyeras et al., 2009[245]	Caloyeras et al., 2012[246]	Zarco et al., 2014[247]
Structure										
1.	Is there a clear statement of the decision problem?	Y	Y	Y	Y	Y	Y	Y	Y	Y
2.	Is the objective of the model specified and consistent with the stated decision problem?	Y	Y	Y	Y	Y	Y	Y	Y	Y
3.	Is the primary decision maker specified?	Y	Y	Y	Y	Y	Y	Y	Y	Y
4.	Is the perspective of the model stated clearly?	Y	Y	Y	Y	Y	Y	Y	Y	Y
5.	Are the model inputs consistent with the stated perspective?	Y	Y	Y	UNC	UNC	Y	Y	Y	Y
6.	Has the scope of the model been stated and justified?	Y	Y	Y	UNC	UNC	Y	UNC	Y	Y
7.	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Y	Y	Y	Y	UNC	UNC	UNC	Y	Y

Philips' criteria		Studies								
		Fredrikson et al., 2013[239]	Iskedjian et al., 2005[242]	Lazzaro et al., 2009[241]	Kobelt et al., 2007[240]	Arbizu et al., 2009[243]	Caloyeras et al., 2008[244]	Caloyeras et al., 2009[245]	Caloyeras et al., 2012[246]	Zarco et al., 2014[247]
8.	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Y	Y	Y	UNC	UNC	UNC	UNC	Y	N
9.	Are the sources of the data used to develop the structure of the model specified?	Y	Y	Y	UNC	UNC	Y	UNC	Y	Y
10.	Are the causal relationships described by the model structure justified appropriately?	Y	Y	Y	UNC	UNC	UNC	UNC	Y	UNC
11.	Are the structural assumptions transparent and justified?	Y	Y	Y	UNC	UNC	UNC	UNC	Y	UNC
12.	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Y	Y	Y	UNC	UNC	UNC	UNC	Y	UNC
13.	Is there a clear definition of the options under evaluation?	Y	Y	Y	Y	Y	Y	Y	Y	Y
14.	Have all feasible and practical options been evaluated?	N	N	N	N	Y	Y	Y	N	N
15.	Is there justification for the exclusion of feasible options?	N	N	N	N	UNC	N/A	UNC	N	N
16.	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?	Y	Y	Y	Y	Y	Y	Y	Y	N
17.	Is the time horizon of the model sufficient to reflect all important differences between the options?	Y	N	Y	Y	Y	Y	Y	Y	N
18.	Are the time horizon of the model, the duration of treatment	Y	Y	Y	UNC	Y	Y	Y	Y	Y

Philips' criteria		Studies								
		Fredrikson et al., 2013[239]	Iskedjian et al., 2005[242]	Lazzaro et al., 2009[241]	Kobelt et al., 2007[240]	Arbizu et al., 2009[243]	Caloyeras et al., 2008[244]	Caloyeras et al., 2009[245]	Caloyeras et al., 2012[246]	Zarco et al., 2014[247]
	and the duration of treatment described and justified?									
19.	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Y	Y	Y	UNC	Y	Y	Y	Y	N
20.	Is the cycle length defined and justified in terms of the natural history of disease?	Y	Y	Y	N	Y	Y	Y	Y	N/A
Data										
21.	Are the data identification methods transparent and appropriate given the objectives of the model?	Y	Y	Y	UNC	UNC	UNC	UNC	Y	UNC
22.	Where choices have been made between data sources are these justified appropriately?	N	N	N	UNC	UNC	UNC	UNC	Y	UNC
23.	Has particular attention been paid to identifying data for the important parameters of the model?	UNC	Y	Y	UNC	UNC	UNC	UNC	UNC	UNC
24.	Has the quality of the data been assessed appropriately?	UNC	N	N	UNC	UNC	UNC	UNC	UNC	UNC
25.	Where expert opinion has been used are the methods described and justified?	Y	Y	Y	UNC	UNC	UNC	UNC	N	UNC
26.	Is the data modelling methodology based on justifiable	Y	Y	Y	UNC	UNC	UNC	UNC	Y	UNC

Philips' criteria		Studies								
		Fredrikson et al., 2013[239]	Iskedjian et al., 2005[242]	Lazzaro et al., 2009[241]	Kobelt et al., 2007[240]	Arbizu et al., 2009[243]	Caloyeras et al., 2008[244]	Caloyeras et al., 2009[245]	Caloyeras et al., 2012[246]	Zarco et al., 2014[247]
	statistical and epidemiological techniques?									
27.	Is the choice of baseline data described and justified?	Y	Y	Y	UNC	UNC	UNC	UNC	Y	Y
28.	Are transition probabilities calculated appropriately?	Y	Y	Y	UNC	UNC	UNC	UNC	Y	UNC
29.	Has a half-cycle correction been applied to both costs and outcomes?	N	N	N	UNC	UNC	UNC	UNC	N	N/A
30.	If not, has the omission been justified?	N	N	N	UNC	UNC	UNC	UNC	N	N/A
31.	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	N	N	N	UNC	UNC	UNC	UNC	Y	UNC
32.	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	Y	Y	Y	UNC	Y	Y	UNC	Y	N/A
33.	Have alternative extrapolation assumptions been explored through sensitivity analysis?	N	N	N	UNC	UNC	UNC	UNC	Y	N/A
34.	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	Y	Y	Y	UNC	UNC	UNC	UNC	Y	N/A
35.	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis	Y	N	N	UNC	UNC	UNC	UNC	UNC	Y

Philips' criteria		Studies								
		Fredrikson et al., 2013[239]	Iskedjian et al., 2005[242]	Lazzaro et al., 2009[241]	Kobelt et al., 2007[240]	Arbizu et al., 2009[243]	Caloyeras et al., 2008[244]	Caloyeras et al., 2009[245]	Caloyeras et al., 2012[246]	Zarco et al., 2014[247]
36.	Are the costs incorporated into the model justified?	Y	Y	Y	Y	Y	Y	Y	Y	Y
37.	Has the source for all costs been described?	Y	Y	Y	N	UNC	UNC	UNC	Y	Y
38.	Have discount rates been described and justified given the target decision maker?	Y	Y	Y	Y	Y	Y	Y	Y	Y
39.	Are the utilities incorporated into the model appropriate?	UNC	Y	Y	Y	Y	Y	Y	Y	Y
40.	Is the source of utility weights referenced?	Y	Y	Y	N	UNC	Y	UNC	Y	Y
41.	Are the methods of derivation for the utility weights justified?	Y	Y	N	N	UNC	UNC	UNC	Y	UNC
42.	Have all data incorporated into the model been described and referenced in sufficient detail?	Y	Y	N	N	UNC	UNC	UNC	Y	N
43.	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?)	Y	Y	Y	N	UNC	UNC	UNC	Y	UNC
44.	Is the process of data incorporation transparent?	UNC	UNC	Y	N	UNC	UNC	UNC	UNC	N
45.	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	N	N	N	N	UNC	UNC	UNC	N	Y
46.	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	N	N	N	N	UNC	UNC	UNC	N	UNC

Philips' criteria		Studies								
		Fredrikson et al., 2013[239]	Iskedjian et al., 2005[242]	Lazzaro et al., 2009[241]	Kobelt et al., 2007[240]	Arbizu et al., 2009[243]	Caloyeras et al., 2008[244]	Caloyeras et al., 2009[245]	Caloyeras et al., 2012[246]	Zarco et al., 2014[247]
47.	Have the four principal types of uncertainty been addressed?	N	N	N	N	UNC	UNC	UNC	N	N
48.	If not, has the omission of particular forms of uncertainty been justified?	N	N	N	N	UNC	UNC	UNC	UNC	N
49.	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	Y	Y	Y	UNC	UNC	UNC	UNC	N	N
50.	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	N	N	N	N	UNC	UNC	UNC	N	N
51.	Has heterogeneity been dealt with by running the model separately for different sub-groups?	N/A	N/A	N/A	UNC	UNC	UNC	UNC	N	N
52.	Are the methods of assessment of parameter uncertainty appropriate?	Y	Y	Y	Y	UNC	UNC	UNC	Y	Y
53.	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Y	Y	Y	UNC	UNC	UNC	UNC	N/A	Y
54.	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	UNC	UNC	UNC	UNC	UNC	UNC	UNC	UNC	N
55.	Are any counterintuitive results from the model explained and justified?	N/A	Y	N/A	UNC	UNC	UNC	UNC	UNC	N/A

Philips' criteria		Studies								
		Fredrikson et al., 2013[239]	Iskedjian et al., 2005[242]	Lazzaro et al., 2009[241]	Kobelt et al., 2007[240]	Arbizu et al., 2009[243]	Caloyeras et al., 2008[244]	Caloyeras et al., 2009[245]	Caloyeras et al., 2012[246]	Zarco et al., 2014[247]
56.	If the model has been calibrated against independent data, have any differences been explained and justified?	N/A	N/A	N/A	UNC	UNC	UNC	UNC	N/A	UNC
57.	Have the results been compared with those of previous models and any differences in results explained?	Y	Y	Y	UNC	UNC	UNC	UNC	N	Y

N- No; N/A- Not Applicable; Y- Yes; UNC-Unclear

25 Appendix 7: Cost-effectiveness review of relapsing remitting multiple sclerosis studies

25.1 *Full record of searches*

25.1.1 Main searches: 2012 to 2016 searches

Medline (Ovid), searched 05/04/2016

Exact database: Ovid MEDLINE(R) 1946 to March Week 4 2016

1	exp Multiple Sclerosis/	47422
2	multiple sclerosis.tw.	50604
3	1 or 2	58051
4	exp Economics/	522024
5	exp "Costs and Cost Analysis"/	195358
6	exp Quality-Adjusted Life Years/	8146
7	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	484557
8	(decision adj2 model).tw.	4186
9	("resource use" or resource utili?ation).tw.	9821
10	(qaly* or (generic adj2 (instrument* or measure*)) or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or Health Utilities Index or HUI or 15D or Assessment of Quality of Life or AQOL or Quality of Well-Being or QWB).tw.	27152
11	4 or 5 or 6 or 7 or 8 or 9 or 10	885600
12	3 and 11	1860
13	limit 12 to yr="2012 -Current"	507

Medline In-Process & Other Non-Indexed Citations (Ovid), searched 05/04/2016

Exact database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations April 04, 2016

1	multiple sclerosis.tw.	4995
2	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	71051
3	(decision adj2 model).tw.	511
4	("resource use" or resource utili?ation).tw.	1438
5	(qaly* or (generic adj2 (instrument* or measure*)) or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or Health Utilities Index or HUI or 15D or Assessment of Quality of Life or AQOL or Quality of Well-Being or QWB).tw.	3483
6	quality-adjusted life year*.tw.	945
7	2 or 3 or 4 or 5 or 6	74406
8	1 and 7	239
9	limit 8 to yr="2012 -Current"	198

Embase (Ovid), searched 05/04/2016

Exact database: Embase 1974 to 2016 Week 14

1	multiple sclerosis/	94999
2	multiple sclerosis.tw.	81514
3	1 or 2	102763
4	exp *health economics/	212668
5	exp quality adjusted life year/	15786
6	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).ti.	164671
7	(decision adj2 model).tw.	6901
8	("resource use" or resource utili?ation).tw.	17938
9	(qaly* or (generic adj2 (instrument* or measure*)) or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or Health Utilities Index or HUI or 15D or Assessment of Quality of Life or AQOL or Quality of Well-Being or QWB).tw.	50631
10	4 or 5 or 6 or 7 or 8 or 9	371080
11	3 and 10	2024
12	limit 11 to yr="2012 -Current"	988
13	limit 12 to (conference abstract or conference paper or conference proceeding or "conference review")	550
14	12 not 13	438

NHS EED and HTA database (Cochrane Library), searched 05/04/2016

ID	Search	Hits
#1	MeSH descriptor: [Multiple Sclerosis] explode all trees	2127
#2	multiple sclerosis:ti,ab,kw	5131
#3	#1 or #2 Publication Year from 2012 to 2016	2064

Total all databases: 2064

Technology Assessments: 30

Economic Evaluations: 27

Science Citation Index (Web of Knowledge), searched 05/04/2016

# 7	315	#5 not #6 *Indexes=SCI-EXPANDED Timespan=2012-2016*
# 6	157	(#5) *AND* DOCUMENT TYPES: (Meeting Abstract OR Meeting Summary OR Proceedings Paper) *Indexes=SCI-EXPANDED Timespan=2012-2016*
# 5	472	#4 AND #1 *Indexes=SCI-EXPANDED Timespan=2012-2016*
# 4	73,283	#3 OR #2 *Indexes=SCI-EXPANDED Timespan=2012-2016*
# 3	24,433	TS=((“quality adjusted life” NEAR/1 year*) or QALY* or (generic NEAR/2 (instrument* or measure*)) or euro-qol or euroqol or “euro qol” or EQ5D or EQ-5D or SF-36 or SF36 or SF-6D or SF6D or "health utilities index" or HUI or 15D or

		"assessment of quality of life" or AQOL or "Quality of Well-Being" or QWB or (decision NEAR/2 model*) or “resource use” or (resource NEAR/1 utili?ation)) *Indexes=SCI-EXPANDED Timespan=2012-2016*
# 2	53,184	TI=(cost* or economic* or pharmacoeconomic* or pharmaco-economic*) *Indexes=SCI-EXPANDED Timespan=2012-2016*
# 1	87,043	TS="multiple sclerosis" *Indexes=SCI-EXPANDED Timespan=All years*

RePEc, searched 05/04/2016

EconPapers

Free text: "multiple sclerosis"

128

Sorted by item date

Total number published from 2012 to 2016: 32

CEA Registry, searched 05/04/2016

Contained details of articles up to 2014 at time of search

Basic Search

Articles

Full Search Contents: multiple sclerosis

Total number published from 2012 to 2016: 17

ScHARR HUD, searched 05/04/2016

multiple sclerosis in any field

AND

2012 to 2016 in Year Published

Total: 7

25.1.2 Main searches: HRQoL studies with generic measures up to 2011

Medline (Ovid), searched 06/04/2016

Exact database: Ovid MEDLINE(R) 1946 to March Week 4 2016

1	exp Multiple Sclerosis/	47422
2	multiple sclerosis.tw.	50604
3	1 or 2	58051
4	(qaly* or (generic adj2 (instrument* or measure*)) or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or Health Utilities Index or HUI or 15D or Assessment of Quality of Life or AQOL or Quality of Well-Being or QWB).tw.	27152

5	3 and 4	355
6	limit 5 to yr="1902 - 2011"	248

Medline In-Process & Other Non-Indexed Citations (Ovid), searched 06/04/2016

Exact database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations April 05, 2016

1	multiple sclerosis.tw.	5010
2	(qaly* or (generic adj2 (instrument* or measure*)) or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or Health Utilities Index or HUI or 15D or Assessment of Quality of Life or AQOL or Quality of Well-Being or QWB).tw.	3504
3	1 and 2	46
4	limit 3 to yr="1860 - 2011"	7

Embase (Ovid), searched 06/04/2016

Exact database: Embase 1974 to 2016 Week 14

1	multiple sclerosis/	94999
2	multiple sclerosis.tw.	81514
3	1 or 2	102763
4	(qaly* or (generic adj2 (instrument* or measure*)) or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or Health Utilities Index or HUI or 15D or Assessment of Quality of Life or AQOL or Quality of Well-Being or QWB).tw.	50631
5	3 and 4	885
6	limit 5 to yr="1902 - 2011"	427
7	limit 6 to (conference abstract or conference paper or conference proceeding or "conference review")	158
8	6 not 7	269

Science Citation Index (Web of Knowledge), searched 06/04/2016

# 5	332	#3 not #4 *Indexes=SCI-EXPANDED Timespan=1900-2011*
# 4	19	(#3) *AND* DOCUMENT TYPES: (Meeting Abstract OR Meeting Summary OR Proceedings Paper) *Indexes=SCI-EXPANDED Timespan=1900-2011*
# 3	351	#2 AND #1 *Indexes=SCI-EXPANDED Timespan=1900-2011*
# 2	20,713	TS=(QALY* or (generic NEAR/2 (instrument* or measure*)) or euro-qol or euroqol or “euro qol” or EQ5D or EQ-5D or SF-36 or SF36 or SF-6D or SF6D or "health utilities index" or HUI or 15D or "assessment of quality of life" or AQOL or "Quality of Well-Being" or QWB) *Indexes=SCI-EXPANDED Timespan=1900-2011*
# 1	61,623	TS="multiple sclerosis" *Indexes=SCI-EXPANDED Timespan=1900-2011*

CEA Registry, searched 06/04/2016

Contains details of articles up to 2014 at time of search

Basic Search

Articles

Full Search Contents: multiple sclerosis

Total number published from 1997 to 2011: 22

ScHARR HUD, searched 06/04/2016

multiple sclerosis in any field

AND

2000 to 2011 in Year Published

Total: 2

25.1.3 Additional searches

Targeted database search to identify any additional multiple sclerosis patient registries that include data from before 1995

Medline (Ovid), searched 31/05/2016

1	exp Multiple Sclerosis/	48148
2	multiple sclerosis.tw.	51476
3	1 or 2	58975
4	exp Registries/	67800
5	(registry or registries).tw.	70207
6	(register or registers).tw.	45934
7	4 or 5 or 6	140237
8	3 and 7	755
9	limit 8 to yr="1902 - 2005"	178

25.2 *Excluded studies (cost-effectiveness studies and health related quality of life studies)*

Table 94: Studies excluded from systematic review of cost-effectiveness in RRMS

	Reference	Reason for exclusion
1.	Guia de practica clinica sobre la atencion a las personas con esclerosis multiple. [Clinical practice guideline of care for people with multiple	Non-English language

	sclerosis] Barcelona: Catalan Agency for Health Information, Assessment and Quality (CAHIAQ -formerly CAHTA). 2012.	
2.	Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis. Health Technology Assessment, 2013 ERG report: Cooper, K, Bryant J, Harris P, Loveman E, Jones J, Welch K. Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis: A Single Technology Appraisal. SHTAC, 2013.	Intervention not of interest
3.	Teriflunomide for the treatment of relapsing forms of multiple sclerosis (Project record). 2013 [cited; Available from: http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32013000872/frame.html.	Intervention not of interest
4.	Dimethyl fumarate for the treatment of relapsing remitting multiple sclerosis (Project record). 2013 [cited; Available from: http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32013000873/frame.html.	Intervention not of interest
5.	Abolfazli R, Hosseini A, Gholami K, Javadi MR, Torkamandi H, Emami S. Quality of Life Assessment in Patients with Multiple Sclerosis Receiving Interferon Beta-1a: A Comparative Longitudinal Study of Avonex and Its Biosimilar CinnoVex. *ISRN Neurology*. 2012;2012:786526.	Intervention not of interest
6.	Acaster S, Perard R, Chauhan D, Lloyd AJ. A forgotten aspect of the NICE reference case: an observational study of the health related quality of life impact on caregivers of people with multiple sclerosis. *BMC Health Serv Res*. 2013;13:346.	Not relevant
7.	Ayuso GI. [Multiple sclerosis: socioeconomic effects and impact on quality of life]. *Med Clin (Barc)*. 2014;143 Suppl 3:7-12. Esclerosis multiple: impacto socioeconomico y en la calidad de vida de los pacientes.	Not relevant
8.	Baumstarck K, Butzkueven H, Fernandez O, Flachenecker P, Stecchi S, Idiman E*, et al.* Responsiveness of the Multiple Sclerosis International Quality of Life questionnaire to disability change: a longitudinal study. *Health & Quality of Life Outcomes*. 2013;11:127.	Generic preference-based measure not used
9.	Baumstarck K, Pelletier J, Aghababian V, Reuter F, Klemina I, Berbis J*, et al.* Is the concept of quality of life relevant for multiple sclerosis patients with cognitive impairment? Preliminary results of a cross-sectional study. *PLoS ONE [Electronic Resource]*. 2012;7(1):e30627.	Generic preference-based measure not used
10.	Baumstarck K, Pelletier J, Boucekine M, Auquier P, MusiQo Lsg. Predictors of quality of life in patients with relapsing-remitting multiple sclerosis: a 2-year longitudinal study. *Rev Neurol (Paris)*. 2015;171(2):173-80.	Generic preference-based measure not used
11.	Baumstarck K, Pelletier J, Butzkueven H, Fernandez O, Flachenecker P, Idiman E*, et al.* Health-related quality of life as an independent predictor of long-term disability for patients with relapsing-remitting multiple sclerosis. *Eur J Neurol*. 2013;20(6):907-14, e78-9.	Generic preference-based measure not used
12.	Beckerman H, Kempen JC, Knol DL, Polman CH, Lankhorst GJ, de Groot V. The first 10 years with multiple sclerosis: the longitudinal course of daily functioning. *J Rehabil Med*. 2013;45(1):68-75.	Generic preference-based measure not used
13.	Bergvall N, Tambour M, Henriksson F, Fredrikson S. Cost-minimization analysis of fingolimod compared with natalizumab for the treatment of relapsing-remitting multiple sclerosis in Sweden. *J Med Econ*. 2013;16(3):349-57.	Intervention not of interest
14.	Boeru G, Milanov I, De Robertis F, Kozubski W, Lang M, Rojas-Farreras S*, et al.* ExtaviJect 30G device for subcutaneous self-injection of interferon beta-1b for multiple sclerosis: a prospective European study. *Medical Devices Evidence and Research*. 2013;6:175-84.	Not relevant
15.	Boucekine M, Loundou A, Baumstarck K, Minaya-Flores P, Pelletier J, Ghattas B*, et al.* Using the random forest method to detect a response shift in the quality of life of multiple sclerosis patients: a cohort study. *BMC Med*	Generic preference-based measure not used

	Res Methodol. 2013;13:20.	
16.	Brandes DW, Raimundo K, Agashivala N, Kim E. Implications of real-world adherence on cost-effectiveness analysis in multiple sclerosis. *J Med Econ*. 2013;16(4):547-51.	Not relevant
17.	Brown MG. Cost of disease-modifying therapies for multiple sclerosis. *Neurology*. 2015;84(21):e181-5.	Not a full economic analysis
18.	Buchanan RJ, Johnson O, Zuniga MA, Carrillo-Zuniga G, Chakravorty BJ. Health-related quality of life among Latinos with multiple sclerosis. *Journal of Social Work in Disability & Rehabilitation*. 2012;11(4):240-57.	Generic preference-based measure not used
19.	Buhse M, Della Ratta C, Galiczewski J, Eckardt P. Caregivers of older persons with multiple sclerosis: determinants of health-related quality of life. *J Neurosci Nurs*. 2015;47(2):E2-E12.	Not relevant
20.	Calkwood J, Cree B, Crayton H, Kantor D, Steingo B, Barbato L*, et al.* Impact of a switch to fingolimod versus staying on glatiramer acetate or beta interferons on patient- and physician-reported outcomes in relapsing multiple sclerosis: Analyses of the EPOC trial. *BMC Neurol*. 2014;14 (1) (no pagination)(220).	Intervention not of interest
21.	Caloyeras JP, Zhang B, Wang C, Eriksson M, Fredrikson S, Beckmann K, et al. Cost-effectiveness analysis of interferon beta-1b for the treatment of patients with a first clinical event suggestive of multiple sclerosis. Clin Ther. 2012;34(5):1132-44	Not relevant for RRMS review
22.	Campbell JD, Ghushchyan V, Brett McQueen R, Cahoon-Metzger S, Livingston T, Vollmer T*, et al.* Burden of multiple sclerosis on direct, indirect costs and quality of life: National US estimates. *Multiple Sclerosis and Related Disorders*. 2014;3(2):227-36.	Results not reported by EDSS level
23.	Campbell JD, McQueen RB, Miravalle A, Corboy JR, Vollmer TL, Nair K. Comparative effectiveness of early natalizumab treatment in JC virus-negative relapsing-remitting multiple sclerosis. *Am J Manag Care*. 2013;19(4):278-85.	Intervention not of interest
24.	Carlson JJ, Hansen RN, Dmochowski RR, Globe DR, Colayco DC, Sullivan SD. Estimating the cost-effectiveness of onabotulinumtoxinA for neurogenic detrusor overactivity in the United States. *Clin Ther*. 2013;35(4):414-24.	Intervention not of interest
25.	Chruzander C, Ytterberg C, Gottberg K, Einarsson U, Widen Holmqvist L, Johansson S. A 10-year follow-up of a population-based study of people with multiple sclerosis in Stockholm, Sweden: changes in health-related quality of life and the value of different factors in predicting health-related quality of life. *J Neurol Sci*. 2014;339(1-2):57-63.	Results not reported by EDSS level
26.	Cioncoloni D, Innocenti I, Bartalini S, Santarnecchi E, Rossi S, Rossi A*, et al.* Individual factors enhance poor health-related quality of life outcome in multiple sclerosis patients. Significance of predictive determinants. *J Neurol Sci*. 2014;345(1-2):213-9.	Generic preference-based measure not used
27.	Coleman CI, Sidovar MF, Roberts MS, Kohn C. Impact of mobility impairment on indirect costs and health-related quality of life in multiple sclerosis. *PLoS ONE [Electronic Resource]*. 2013;8(1):e54756.	Generic measure not used; indirect costs estimated
28.	Crespo C, Izquierdo G, Garcia-Ruiz A, Granell M, Brosa M. Cost minimisation analysis of fingolimod vs natalizumab as a second line of treatment for relapsing-remitting multiple sclerosis. *Neurologia*. 2014;29(4):210-7.	Interventions not of interest
29.	de la Rosa RS, García-Bujalance L, Meca-Lallana J. Cost analysis of glatiramer acetate versus interferon-ß for relapsing-remitting multiple sclerosis in patients with spasticity: the Escala study. *Health Economics Review*. 2015;5(1):1-9.	No decision analytical model
30.	Devy R, Lehert P, Varlan E, Genty M, Edan G. A short and validated multiple sclerosis-specific health-related quality of life measurement for routine medical practice. *Eur J Neurol*. 2013;20(6):935-41.	Generic preference-based measure not used
31.	Di Filippo M, Proietti S, Gaetani L, Gubbiotti M, Di Gregorio M, Eusebi P*, et al.* Lower urinary tract symptoms and urodynamic dysfunction in clinically	Generic preference-based

	isolated syndromes suggestive of multiple sclerosis. *Eur J Neurol*. 2014;21(4):648-53.	measure not used
32.	Ertekin O, Ozakbas S, Idiman E. Caregiver burden, quality of life and walking ability in different disability levels of multiple sclerosis. *NeuroRehabilitation*. 2014;34(2):313-21.	Generic preference-based measure not used
33.	Fernandez-Munoz JJ, Moron-Verdasco A, Cigaran-Mendez M, Munoz-Hellin E, Perez-de-Heredia-Torres M, Fernandez-de-las-Penas C. Disability, quality of life, personality, cognitive and psychological variables associated with fatigue in patients with multiple sclerosis. *Acta Neurol Scand*. 2015;132(2):118-24.	Generic preference-based measure not used
34.	Fiest KM, Fisk JD, Patten SB, Tremlett H, Wolfson C, Warren S*, et al.* Comorbidity is associated with pain-related activity limitations in multiple sclerosis. *Multiple Sclerosis and Related Disorders*. 2015;4(5):470-6.	Not relevant
35.	Fines P, Garner R, Bancej C, Bernier J, Manuel DG. Development and implementation of microsimulation models of neurological conditions. *Health Rep*. 2016;27(3):3-9.	Not relevant
36.	Flensner G, Landtblom AM, Soderhamn O, Ek AC. Work capacity and health-related quality of life among individuals with multiple sclerosis reduced by fatigue: a cross-sectional study. *BMC Public Health*. 2013;13:224.	Generic preference-based measure not used
37.	Fogarty E, Walsh C, Adams R, McGuigan C, Barry M, Tubridy N. Relating health-related Quality of Life to disability progression in multiple sclerosis, using the 5-level EQ-5D. *Mult Scler*. 2013;19(9):1190-6.	No decision analytical model
38.	Fredrikson S, McLeod E, Henry N, Pitcher A, Lowin J, Cuche M, et al. A cost-effectiveness analysis of subcutaneous interferon beta-1a 44mcg 3-times a week vs no treatment for patients with clinically isolated syndrome in Sweden. J Med Econ. 2013;16(6):756-62.	Not relevant for RRMS review
39.	Garattini L, Ghislandi F, Da Costa MR. Cost-Effectiveness Modeling in Multiple Sclerosis: Playing Around with Non-Healthcare Costs? *Pharmacoeconomics*. 2015;33(12):1241-4.	Not relevant
40.	Gavelova M, Nagyova I, Rosenberger J, Krokavcova M, Gdovinova Z, Groothoff JW*, et al.* Importance of an individual's evaluation of functional status for health-related quality of life in patients with multiple sclerosis. *Disability & Health Journal*. 2015;8(3):372-9.	Generic preference-based measure not used
41.	Ghajarzadeh M, Azizi S, Moghadasi AN, Sahraian MA, Azimi A, Mohammadifar M*, et al.* Validity and Reliability of the Persian Version of the PERception de la Scle'rose En Plaques et de ses Pousse'es Questionnaire Evaluating Multiple Sclerosis-related Quality of Life. *Int J Prev Med*. 2016;7:25.	Generic preference-based measure not used
42.	Giordano A, Ferrari G, Radice D, Randi G, Bisanti L, Solari A*, et al.* Health-related quality of life and depressive symptoms in significant others of people with multiple sclerosis: a community study. *Eur J Neurol*. 2012;19(6):847-54.	Not relevant
43.	Goodwin E, Green C. A Quality-Adjusted Life-Year Measure for Multiple Sclerosis: Developing a Patient-Reported Health State Classification System for a Multiple Sclerosis-Specific Preference-Based Measure. *Value Health*. 2015;18(8):1016-24.	Generic preference-based measure not used
44.	Goodwin E, Green C, Spencer A. Estimating a Preference-Based Index for an Eight-Dimensional Health State Classification System for Multiple Sclerosis. *Value Health*. 2015;18(8):1025-36.	Generic preference-based measure not used
45.	Grytten N, Aarseth JH, Espeset K, Berg Johnsen G, Wehus R, Lund C*, et al.* Health-related quality of life and disease-modifying treatment behaviour in relapsing-remitting multiple sclerosis--a multicentre cohort study. *Acta Neurol Scand*. 2012;Supplementum.(195):51-7.	Generic preference-based measure not used
46.	Hadianfard H, Ashjazadeh N, Feridoni S, Farjam E. The role of psychological resilience, severity of disease and treatment adherence in the prediction of health-related quality of life in patients with multiple sclerosis.	Generic preference-based measure not used

	Neurology Asia. 2015;20(3):263-8.	
47.	Hawton A, Green C, Telford C, Zajicek J, Wright D. Using the Multiple Sclerosis Impact Scale to estimate health state utility values: mapping from the MSIS-29, version 2, to the EQ-5D and the SF-6D. *Value Health*. 2012;15(8):1084-91.	Excluded from systematic review, but retained for information on inputs
48.	Hawton A, Green C, Telford CJ, Wright DE, Zajicek JP. The use of multiple sclerosis condition-specific measures to inform health policy decision-making: mapping from the MSWS-12 to the EQ-5D. *Mult Scler*. 2012;18(6):853-61.	Excluded from systematic review, but retained for information on inputs
49.	Heisen M, Treur MJ, van der Hel WS, Frequin ST, Groot MT, Verheggen BG. Fingolimod reduces direct medical costs compared to natalizumab in patients with relapsing-remitting multiple sclerosis in The Netherlands. *J Med Econ*. 2012;15(6):1149-58.	Interventions not of interest; not full economic analysis
50.	Jones KH, Ford DV, Jones PA, John A, Middleton RM, Lockhart-Jones H*, et al.* How people with multiple sclerosis rate their quality of life: an EQ-5D survey via the UK MS register. *PLoS ONE [Electronic Resource]*. 2013;8(6):e65640.	Excluded from systematic review, but retained for information on inputs
51.	Kappos L, Gold R, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K*, et al.* Quality of life outcomes with BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: the DEFINE study. *Mult Scler*. 2014;20(2):243-52.	Not relevant
52.	Karampampa K, Gustavsson A, Miltenburger C, Eckert B. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from five European countries. *Mult Scler*. 2012;18(2 Suppl):7-15.	Excluded from systematic review, but retained for information on inputs
53.	Karampampa K, Gustavsson A, Miltenburger C, Kindundu CM, Selchen DH. Treatment experience, burden, and unmet needs (TRIBUNE) in multiple sclerosis: the costs and utilities of MS patients in Canada. *J Popul Ther Clin Pharmacol*. 2012;19(1):e11-25.	Excluded from systematic review, but retained for information on inputs
54.	Karampampa K, Gustavsson A, Miltenburger C, Kindundu CM, Selchen DH. Treatment experience, burden, and unmet needs (Tribune) in multiple sclerosis study: The costs and utilities of MS patients in Canada. *J Popul Ther Clin Pharmacol*. 2012;19(1):11-25.	Excluded from systematic review, but retained for information on inputs
55.	Karampampa K, Gustavsson A, Miltenburger C, Mora S, Arbizu T. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from Spain. *Mult Scler*. 2012;18(2 Suppl):35-9.	Excluded from systematic review, but retained for information on inputs
56.	Karampampa K, Gustavsson A, Miltenburger C, Neidhardt K, Lang M. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from Germany. *Mult Scler*. 2012;18(2 Suppl):23-7.	Excluded from systematic review, but retained for information on inputs
57.	Karampampa K, Gustavsson A, Miltenburger C, Teruzzi C, Fattore G. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from Italy. *Mult Scler*. 2012;18(2 Suppl):29-34.	Excluded from systematic review, but retained for information on inputs
58.	Karampampa K, Gustavsson A, Miltenburger C, Tyas D. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from the United Kingdom. *Mult Scler*. 2012;18(2 Suppl):41-5.	Excluded from systematic review, but retained for information on

		inputs
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MS HRQoL generic measures up to 2011 1 or 1,3 or unsure for full text screen

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60.	Miller A, Dishon S. Health-related quality of life in multiple sclerosis: The impact of disability, gender and employment status. *Qual Life Res*. 2006;15(2):259-71.	No generic preference-based measure used
61.	Mo F, Choi BC, Li FC, Merrick J. Using Health Utility Index (HUI) for measuring the impact on health-related quality of Life (HRQL) among individuals with chronic diseases. *Thescientificworldjournal*. 2004;4:746-57.	Mixed population
62.	Moore F, Wolfson C, Alexandrov L, Lapierre Y. Do general and multiple sclerosis-specific quality of life instruments differ? *Can J Neurol Sci*. 2004;31(1):64-71.	HRQoL results grouped by EDSS levels
63.	Morales Rde R, Morales Nde M, Rocha FC, Fenelon SB, Pinto Rde M, Silva CH. [Health-related quality of life in multiple sclerosis]. *Arq Neuropsiquiatr*. 2007;65(2B):454-60. Qualidade de vida em portadores de esclerose multipla.	No generic preference-based measure used
64.	Murrell RC, Kenealy PM, Beaumont JG, Lintern TC. Assessing quality of life in persons with severe neurological disability associated with multiple sclerosis: The psychometric evaluation of two quality of life measures. *Br J Health Psychol*. 1999;4(4):349-62.	No generic preference-based measure used
65.	Myers JA, McPherson KM, Taylor WJ, Weatherall M, McNaughton HK. Duration of condition is unrelated to health-state valuation on the EuroQoL. *Clin Rehabil*. 2003;17(2):209-15.	Not relevant
66.	Nicholl CR, Lincoln NB, Francis VM, Stephan TF. Assessing quality of life in people with multiple sclerosis. *Disabil Rehabil*. 2001;23(14):597-603.	Results not presented by EDSS levels
67.	Nicholl L, Hobart JC, Cramp AFL, Lowe-Strong AS. Measuring quality of life in multiple sclerosis: not as simple as it sounds. *Mult Scler*. 2005;11(6):708-12.	No generic preference-based measure used
68.	Nortvedt MW, Riise T, Myhr KM, Nyland HI. Quality of life in multiple sclerosis: measuring the disease effects more broadly. *Neurology*. 1999;53(5):1098-103.	Intervention is not of interest

69.	Nortvedt MW, Riise T, Myhr KM, Nyland HI. Performance of the SF-36, SF-12, and RAND-36 summary scales in a multiple sclerosis population. *Med Care*. 2000;38(10):1022-8.	No generic preference-based measure used
70.	Nortvedt MW, Riise T, Myhr KM, Nyland HI. Quality of life as a predictor for change in disability in MS. *Neurology*. 2000;55(1):51-4.	No generic preference-based measure used
71.	Nortvedt MW, Riise T, Myhr KM, Nyland HI, Hanestad BR. Type I interferons and the quality of life of multiple sclerosis patients. Results from a clinical trial on interferon alfa-2a. *Mult Scler*. 1999;5(5):317-22.	Intervention is not of interest
72.	Noyes K, Bajorska A, Chappel A, Schwid SR, Mehta LR, Weinstock-Guttman B*, et al.* Cost-effectiveness of disease-modifying therapy for multiple sclerosis: a population-based study. *Neurology*. 2011;77(4):355-63.	Economic analysis pre-2012
73.	Nuijten MJ, Hutton J. Cost-effectiveness analysis of interferon beta in multiple sclerosis: a Markov process analysis. *Value Health*. 2002;5(1):44-54.	Economic analysis pre-2012
74.	Orme M, Kerrigan J, Tyas D, Russell N, Nixon R. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. *Value Health*. 2007;10(1):54-60.	Excluded from systematic review, but retained for information on inputs
75.	Ozakbas S, Akdede BB, Kosehasanogullari G, Aksan O, Idiman E. Difference between generic and multiple sclerosis-specific quality of life instruments regarding the assessment of treatment efficacy. *J Neurol Sci*. 2007;256(1-2):30-4.	Not relevant
76.	Pakpour AH, Yekaninejad MS, Mohammadi NK, Molsted S, Zarei F, Patti F*, et al.* Health-related quality of life in Iranian patients with multiple sclerosis: a cross-cultural study. *Neurol Neurochir Pol*. 2009;43(6):517-26.	No generic preference-based measure used
77.	Parkin D, Jacoby A, McNamee P, Miller P, Thomas S, Bates D. Treatment of multiple sclerosis with interferon beta: an appraisal of cost-effectiveness and quality of life. *J Neurol Neurosurg Psychiatry*. 2000;68(2):144-9.	Economic analysis pre-2012
78.	Parkin D, McNamee P, Jacoby A, Miller P, Thomas S, Bates D. A cost-utility analysis of interferon beta for multiple sclerosis. *Health Technol Assess*. 1998;2(4):1-45.	Economic analysis pre-2012
79.	Parkin D, Rice N, Jacoby A, Doughty J. Use of a visual analogue scale in a daily patient diary: modelling cross-sectional time-series data on health-related quality of life. *Soc Sci Med*. 2004;59(2):351-60.	Not relevant
80.	Patti F, Amato MP, Battaglia MA, Pitaro M, Russo P, Solaro C*, et al.* Caregiver quality of life in multiple sclerosis: a multicentre Italian study. *Mult Scler*. 2007;13(3):412-9.	Not relevant
81.	Patti F, Cacopardo M, Palermo F, Ciancio MR, Lopes R, Restivo D*, et al.* Health-related quality of life and depression in an Italian sample of multiple sclerosis patients. *J Neurol Sci*. 2003;211(1-2):55-62.	Cargiver quality of life
82.	Patti F, Russo P, Pappalardo A, Macchia F, Civalleri L, Paolillo A*, et al.* Predictors of quality of life among patients with multiple sclerosis: An Italian cross-sectional study. *J Neurol Sci*. 2007;252(2):121-9.	Not relevant
83.	Pfennings L, Cohen L, Ader H, Polman C, Lankhorst G, Smits R*, et al.* Exploring differences between subgroups of multiple sclerosis patients in health-related quality of life. *J Neurol*. 1999;246(7):587-91.	Not relevant

84.	Pfennings LE, Van der Ploeg HM, Cohen L, Bramsen I, Polman CH, Lankhorst GJ*, et al.* A health-related quality of life questionnaire for multiple sclerosis patients. *Acta Neurol Scand*. 1999;100(3):148-55.	No generic preference-based measure used
85.	Phillips CJ. The cost of multiple sclerosis and the cost effectiveness of disease-modifying agents in its treatment. *CNS Drugs*. 2004;18(9):561-74.	Economic analysis pre-2012
86.	Phillips CJ, Gilmour L, Gale R, Palmer M. A cost utility model of interferon beta-1b in the treatment of relapsing-remitting multiple sclerosis. *J Med Econ*. 2001;4(35-50):35-50.	Economic analysis pre-2012
87.	Phillips JT, Giovannoni G, Lublin FD, O'Connor PW, Polman CH, Willoughby E*, et al.* Sustained improvement in Expanded Disability Status Scale as a new efficacy measure of neurological change in multiple sclerosis: treatment effects with natalizumab in patients with relapsing multiple sclerosis. *Mult Scler*. 2011;17(8):970-9.	Not relevant
88.	Pittock SJ, Mayr WT, McClelland RL, Jorgensen NW, Weigand SD, Noseworthy JH*, et al.* Quality of life is favorable for most patients with multiple sclerosis: a population-based cohort study. *Arch Neurol*. 2004;61(5):679-86.	No relevant information
89.	Popova EV, Riabukhina OV, Vorob'eva OV, Malkova NA, Boiko AN. Changes in quality of life in patients with remitted multiple sclerosis during the specific treatment with disease-modifying drugs: a comparative study of populations of Moscow and Novosibirsk. *Zhurnal Nevrologii I Psikhiatrii Imeni S S Korsakova*. 2010;110(5):67-70.	No relevant information
90.	Pozzilli C, Palmisano L, Mainero C, Tomassini V, Marinelli F, Ristori G*, et al.* Relationship between emotional distress in caregivers and health status in persons with multiple sclerosis. *Mult Scler*. 2004;10(4):442-6.	Carers' disutilities
91.	Prosser LA, Kuntz KM, Bar-Or A, Weinstein MC. Patient and community preferences for treatments and health states in multiple sclerosis. *Mult Scler*. 2003;9(3):311-9.	Results not reported for all EDSS levels
92.	Prosser LA, Kuntz KM, Bar-Or A, Weinstein MC. Cost-effectiveness of interferon beta-1a, interferon beta-1b, and glatiramer acetate in newly diagnosed non-primary progressive multiple sclerosis. *Value Health*. 2004;7(5):554-68.	Economic analysis pre-2012
93.	Putzki N, Fischer J, Gottwald K, Reifschneider G, Ries S, Siever A*, et al.* Quality of life in 1000 patients with early relapsing-remitting multiple sclerosis. *Eur J Neurol*. 2009;16(6):713-20.	Excluded from systematic review, but retained for information on inputs
94.	Riazi A, Hobart JC, Lamping DL, Fitzpatrick R, Freeman JA, Jenkinson C*, et al.* Using the SF-36 measure to compare the health impact of multiple sclerosis and Parkinson's disease with normal population health profiles. *J Neurol Neurosurg Psychiatry*. 2003;74(6):710-4.	No generic preference-based measure used
95.	Rivera-Navarro J, Benito-Leon J, Oreja-Guevara C, Pardo J, Dib WB, Orts E*, et al.* Burden and health-related quality of life of Spanish caregivers of persons with multiple sclerosis. *Mult Scler*. 2009;15(11):1347-55.	Carers' disutilities
96.	Robinson D, Jr., Zhao N, Gathany T, Kim LL, Cella D, Revicki D. Health perceptions and clinical characteristics of relapsing-remitting multiple sclerosis patients: baseline data from an international clinical trial. *Curr Med Res Opin*. 2009;25(5):1121-30.	No generic preference-based measure used
97.	Rothwell PM, McDowell Z, Wong CK, Dorman PJ. Doctors and patients don't agree: cross sectional study of patients' and doctors' perceptions and	Not relevant

	assessments of disability in multiple sclerosis. *BMJ*. 1997;314(7094):1580-3.	
98.	Rubio-Terres C, Aristegui Ruiz I, Medina Redondo F, Izquierdo Ayuso G. [Cost-utility analisys of multiple sclerosis treatment with glatiramer acetate or interferon beta in Spain]. *Farmacia Hospitalaria*. 2003;27(3):159-65. Analisis coste utilidad del tratamiento de la esclerosis multiple remitente-recidivante con acetato de glatiramero o interferon beta en Espana.	Economic analysis pre-2012
99.	Rubio-Terres C, Dominguez-Gil Hurle A. [Cost-utility analysis of relapsing-remitting multiple sclerosis treatment with azathioprine or interferon beta in Spain]. *Rev Neurol*. 2005;40(12):705-10. Analisis coste-utilidad del tratamiento de la esclerosis multiple remitente-recidivante con azatioprina o interferon beta en Espana.	Economic analysis pre-2012
100.	Rudick RA, Miller D, Hass S, Hutchinson M, Calabresi PA, Confavreux C*, et al*. Health-related quality of life in multiple sclerosis: effects of natalizumab. *Ann Neurol*. 2007;62(4):335-46.	Intervention is not of interest
101.	Rudick RA, Miller DM. Health-related quality of life in multiple sclerosis - Current evidence, measurement and effects of disease severity and treatment. *Cns Drugs*. 2008;22(10):827-39.	No generic preference-based measure used
102.	Sehanovic A, Dostovic Z, Smajlovic D, Avdibegovic E. Quality of life in patients suffering from Parkinson's disease and multiple sclerosis. *Med Arh*. 2011;65(5):291-4.	No generic preference-based measure used
103.	Senol V, Sipahioglu MH, Ozturk A, Argun M, Utas C. Important determinants of quality of life in a peritoneal dialysis population in Turkey. *Ren Fail*. 2010;32(10):1196-201.	Not relevant
104.	Shawaryn MA, Schiaffino KM, LaRocca NG, Johnston MV. Determinants of health-related quality of life in multiple sderosis: the role of illness intrusiveness. *Mult Scler*. 2002;8(4):310-8.	Utility values not reported
105.	Solari A, Radice D. Health status of people with multiple sclerosis: a community mail survey. *Neurol Sci*. 2001;22(4):307-15.	No generic preference-based measure used
106.	Szilasiova J, Krokavcova M, Gdovinova Z, Rosenberger J, Van Dijk JP. Quality of life in patients with multiple sclerosis in Eastern Slovakia. *Disabil Rehabil*. 2011;33(17-18):1587-93.	No generic preference-based measure used
107.	Tatarinova M, Fokin IV, Boiko AN. [Quality of life in multiple sclerosis and pharmaco-economic studies]. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2002;Suppl:76-80. Kachestvo zhizni bol'nykh rasseiannym sklerozom i nekotorye podkhody k farmakoekonomicheskim issledovaniiam.	Full-text not available in English Language
108.	Thompson JP, Noyes K, Dorsey ER, Schwid SR, Holloway RG. Quantitative risk-benefit analysis of natalizumab. *Neurology*. 2008;71(5):357-64.	Economic analysis pre-2012, but provides useful information on utility values by EDSS
109.	Turpin KV, Carroll LJ, Cassidy JD, Hader WJ. Deterioration in the health-related quality of life of persons with multiple sclerosis: the possible warning signs. *Mult Scler*. 2007;13(8):1038-45.	Not relevant
110.	Vermersch P, de Seze J, Delisse B, Lemaire S, Stojkovic T. Quality of life in multiple sclerosis: influence of interferon-beta1 a (Avonex) treatment. *Mult Scler*. 2002;8(5):377-81.	No generic preference-based measure used

111.	Vickrey BG, Hays RD, Genovese BJ, Myers LW, Ellison GW. Comparison of a generic to disease-targeted health-related quality-of-life measures for multiple sclerosis. *J Clin Epidemiol*. 1997;50(5):557-69.	No generic preference-based measure used
112.	Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW. A health-related quality of life measure for multiple sclerosis. *Qual Life Res*. 1995;4(3):187-206.	No generic preference-based measure used

25.3 *Blank data extraction form for cost-effectiveness studies(relapsing remitting multiple sclerosis)*

Date:
Study ID:
Name of first reviewer:
Name of second reviewer:

Study details	
Study title	
First author	
Co-authors	
Source of publication Journal yy;vol(issue):pp	
Language	
Publication type	
Inclusion criteria/study eligibility/PICOS	
Population	
Intervention(s)	
Comparator(s)	
Outcome(s)	
Study design	
Methods	
Setting and location	
Study perspective	
Comparators	
Time horizon	
Discount rate	
Outcomes	
Measurement of effectiveness	
Measurement and valuation of preference based outcomes	
Resource use and costs	
Currency, price date and conversion	
Model type	
Assumptions	
Analytical methods	
Results	
Study parameters	
Incremental costs and outcomes	
Characterising uncertainty	
Discussion	
Study findings	
Limitations	
Generalisability	
Other	
Source of funding	
Conflicts of interest	
Comments	
Authors conclusion	
Reviewer's conclusion	

25.4 *Quality assessment of model-based cost-effectiveness studies (relapsing remitting multiple sclerosis)*

Table 95: CHEERS quality assessment checklist for economic evaluations in RRMS

Assessment	Studies									
	Sanchez-de la Rosa et al., 2012[248]	Nikfar et al., 2013[249]	Agashivala & Kim, 2012[250]	Palace et al., 2015[149]	Pan et al., 2012[251]	Darbà et al, 2014[252]	Imani et al, 2012[253]	Dembek et al, 2014[254]	Chevalier et al, 2016[255]	Lee et al., 2012[256]
Title	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Abstract	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Introduction										
Background and objectives	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Methods										
Target population and subgroups	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Setting and location	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Study perspective	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Comparators	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Time horizon	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Discount rate	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Choice of health outcomes	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Measurement of effectiveness	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Measurement and valuation of preference-based outcomes	Y	Y	N/A	Y	Y	N/A	N	Y	Y	Y
Estimating resources and costs	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Currency, price date, and conversion	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Choice of model	Y	Y	N	Y	Y	Y	N	Y	Y	Y

Assessment	Studies									
	Sanchez-de la Rosa et al., 2012[248]	Nikfar et al., 2013[249]	Agashivala & Kim, 2012[250]	Palace et al., 2015[149]	Pan et al., 2012[251]	Darbà et al, 2014[252]	Imani et al, 2012[253]	Dembek et al, 2014[254]	Chevalier et al, 2016[255]	Lee et al., 2012[256]
Assumptions	Y	Y	Y	Y	Y	N	N	Y	Y	Y
Analytical methods	Y	Y	N	Y	Y	UNC	N	Y	Y	Y
Results										
Study parameters	Y	Y	N	Y	Y	N	Y	N	N	Y
Incremental costs and outcomes	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Characterising uncertainty	Y	Y	N	Y	Y	N	N	N	Y	N
Discussion										
Study findings	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Limitations	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Generalizability	Y	Y	N	Y	Y	N	Y	Y	N	Y
Other										
Source of funding	Y	Y	Y	Y	Y	Y	UNC	Y	Y	Y
Conflicts of interest	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
N- No; N/A- Not Applicable; Y- Yes; UNC-Unclear										

Table 96: Philips' quality assessment checklist for economic evaluations in RRMS

Philips' criteria		Studies									
		Sanchez-de la Rosa et al., 2012[248]	Nikfar et al., 2013[249]	Agashivala & Kim, 2012[250]	Palace et al., 2015[149]	Pan et al., 2012[251]	Darbà et al, 2014[252]	Imani et al, 2012[253]	Dembek et al, 2014[254]	Chevalier et al, 2016[255]	Lee et al., 2012[256]
STRUCTURE											
1.	Is there a clear statement of the decision problem?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2.	Is the objective of the model specified and consistent with the stated decision problem?	Y	Y	UNC	Y	Y	Y	Y	Y	Y	Y
3.	Is the primary decision maker specified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4.	Is the perspective of the model stated clearly?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
5.	Are the model inputs consistent with the stated perspective?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
6.	Has the scope of the model been stated and justified?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
7.	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
8.	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Y	Y	UNC	Y	Y	UNC	Y	Y	Y	Y
9.	Are the sources of the data used to develop the structure of the model specified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Philips' criteria		Studies									
		Sanchez-de la Rosa et al., 2012[248]	Nikfar et al., 2013[249]	Agashivala & Kim, 2012[250]	Palace et al., 2015[149]	Pan et al., 2012[251]	Darbà et al, 2014[252]	Imani et al, 2012[253]	Dembek et al, 2014[254]	Chevalier et al, 2016[255]	Lee et al., 2012[256]
10.	Are the causal relationships described by the model structure justified appropriately?	Y	Y	UNC	Y	Y	Y	Y	Y	Y	Y
11.	Are the structural assumptions transparent and justified?	Y	Y	UNC	Y	Y	N	Y	Y	Y	Y
12.	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Y	Y	UNC	Y	Y	UNC	Y	Y	Y	Y
13.	Is there a clear definition of the options under evaluation?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
14.	Have all feasible and practical options been evaluated?	Y	N	N	N	N	N	Y	Y	Y	N
15.	Is there justification for the exclusion of feasible options?	N/A	N	UNC	N	N	N	N/A	N/A	N/A	N
16.	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?	Y	Y	UNC	Y	Y	N	Y	Y	Y	Y
17.	Is the time horizon of the model sufficient to reflect all important differences between the options?	N	Y	N	N	Y	Y	Y	Y	Y	N
18.	Are the time horizon of the model, the duration of treatment and the duration of treatment described and justified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
19.	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of	Y	Y	UNC	Y	Y	N	Y	Y	Y	Y

Philips' criteria		Studies									
		Sanchez-de la Rosa et al., 2012[248]	Nikfar et al., 2013[249]	Agashiva la & Kim, 2012[250]	Palace et al., 2015[149]	Pan et al., 2012[251]	Darbà et al, 2014[252]	Imani et al, 2012[253]	Dembek et al, 2014[254]	Chevalier et al, 2016[255]	Lee et al., 2012[256]
	the disease in question and the impact of interventions?										
20.	Is the cycle length defined and justified in terms of the natural history of disease?	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
DATA											
21.	Are the data identification methods transparent and appropriate given the objectives of the model?	Y	Y	Y	Y	N	Y	N	Y	Y	Y
22.	Where choices have been made between data sources are these justified appropriately?	UNC	N	UNC	N	N	Y	N	Y	Y	Y
23.	Has particular attention been paid to identifying data for the important parameters of the model?	UNC	UNC	UNC	UNC	N	N	N	UNC	Y	UNC
24.	Has the quality of the data been assessed appropriately?	N	N	N	N	N	N	N	N	N	N
25.	Where expert opinion has been used are the methods described and justified?	N/A	N/A	N	N/A	N/A	N/A	N/A	N/A	Y	N
26.	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	Y	Y	UNC	Y	N	Y	UNC	N	Y	Y
27.	Is the choice of baseline data described and justified?	Y	Y	Y	Y	Y	Y	UNC	Y	Y	Y

Philips' criteria		Studies									
		Sanchez-de la Rosa et al., 2012[248]	Nikfar et al., 2013[249]	Agashivala & Kim, 2012[250]	Palace et al., 2015[149]	Pan et al., 2012[251]	Darbà et al, 2014[252]	Imani et al, 2012[253]	Dembek et al, 2014[254]	Chevalier et al, 2016[255]	Lee et al., 2012[256]
28.	Are transition probabilities calculated appropriately?	UNC	UNC	UNC	UNC	UNC	UNC	UNC	UNC	UNC	UNC
29.	Has a half-cycle correction been applied to both costs and outcomes?	N/A	N	N	N	N	N	N	N	N	N
30.	If not, has the omission been justified?	N/A	N	N	N	N	N	N	N	N	N
31.	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	UNC	UNC	Y	Y	UNC	Y	UNC	Y	Y	Y
32.	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	N/A	UNC	N/A	N	N	UNC	N	Y	UNC	N
33.	Have alternative extrapolation assumptions been explored through sensitivity analysis?	N/A	N	Y	N/A	N	N	UNC	N	UNC	N
34.	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	N/A	N	N/A	UNC	UNC	UNC	UNC	Y	Y	UNC
35.	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis	N/A	N	N/A	N	N	N	UNC	N	Y	UNC
36.	Are the costs incorporated into the model justified?	Y	Y	Y	Y	Y	N	Y	Y	Y	Y

Philips' criteria		Studies									
		Sanchez-de la Rosa et al., 2012[248]	Nikfar et al., 2013[249]	Agashivala & Kim, 2012[250]	Palace et al., 2015[149]	Pan et al., 2012[251]	Darbà et al, 2014[252]	Imani et al, 2012[253]	Dembek et al, 2014[254]	Chevalier et al, 2016[255]	Lee et al., 2012[256]
37.	Has the source for all costs been described?	Y	Y	Y	Y	Y	Y	UNC	Y	Y	Y
38.	Have discount rates been described and justified given the target decision maker?	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
39.	Are the utilities incorporated into the model appropriate?	Y	Y	N/A	Y	Y	N/A	N	Y	Y	Y
40.	Is the source of utility weights referenced?	Y	Y	N/A	Y	Y	N/A	Y	Y	Y	Y
41.	Are the methods of derivation for the utility weights justified?	Y	Y	N/A	Y	Y	N/A	N	Y	Y	Y
42.	Have all data incorporated into the model been described and referenced in sufficient detail?	N	N	Y	N	N	Y	N	N	Y	Y
43.	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
44.	Is the process of data incorporation transparent?	N	N	Y	N	N	N	N	N	N	Y
45.	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	N	N/A	N/A	N	N	N	UNC	N	N	N
46.	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	N/A	N/A	N/A	N/A	N/A	UNC	UNC	UNC	Y	N

Philips' criteria		Studies									
		Sanchez-de la Rosa et al., 2012[248]	Nikfar et al., 2013[249]	Agashiva la & Kim, 2012[250]	Palace et al., 2015[149]	Pan et al., 2012[251]	Darbà et al, 2014[252]	Imani et al, 2012[253]	Dembek et al, 2014[254]	Chevalier et al, 2016[255]	Lee et al., 2012[256]
47.	Have the four principal types of uncertainty been addressed?	N	N	N	N	N	N	UNC	Y	Y	N
48.	If not, has the omission of particular forms of uncertainty been justified?	N	N	N	N	N	N	UNC	N	N/A	N
49.	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	N	N	N	N	N	N	N	N	N	N
50.	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	N	N	N	N	N	N	N	N	N	N
51.	Has heterogeneity been dealt with by running the model separately for different sub-groups?	N	N	N	N	N	N	N	Y	N	N
52.	Are the methods of assessment of parameter uncertainty appropriate?	Y	Y	UNC	Y	Y	UNC	N	UNC	Y	Y
53.	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Y	Y	UNC	Y	Y	N	N	N	N/A	N
54.	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	N	N	N	N	N	N	N	N	N	N

Philips' criteria		Studies									
		Sanchez-de la Rosa et al., 2012[248]	Nikfar et al., 2013[249]	Agashiva la & Kim, 2012[250]	Palace et al., 2015[149]	Pan et al., 2012[251]	Darbà et al, 2014[252]	Imani et al, 2012[253]	Dembek et al, 2014[254]	Chevalier et al, 2016[255]	Lee et al., 2012[256]
55.	Are any counterintuitive results from the model explained and justified?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Y	N/A	Y
56.	If the model has been calibrated against independent data, have any differences been explained and justified?	N	N	N/A	N/A	N/A	N	N	N	N/A	N
57.	Have the results been compared with those of previous models and any differences in results explained?	Y	Y	N	Y	Y	N	Y	Y	N	Y
N- No; N/A- Not Applicable; Y- Yes; UNC-Unclear											

25.5 *Results of additional searches*

Multiple sclerosis registries

Potentially relevant studies
Bronnum-Hansen, H., et al. (1994). "Survival of patients with multiple sclerosis in Denmark: a nationwide, long-term epidemiologic survey." Neurology 44(10): 1901-1907
Bronnum-Hansen, H., et al. (1995). "[Survival in disseminated sclerosis in Denmark. A nation-wide study of the period 1948-1986]." Ugeskrift for Laeger 157(51): 7131-7135.
Confavreux, C. (1994). "Establishment and use of multiple sclerosis registers--EDMUS." Annals of Neurology 36 Suppl: S136-139.
Flachenecker, P., et al. (2005). "[MS registry in Germany--design and first results of the pilot phase]." Nervenarzt 76(8): 967-975.
A prospective study of the incidence, prevalence and mortality of multiple sclerosis in Leeds." Journal of Neurology 249(3): 260-265.
Koch-Henriksen, N. (1999). "The Danish Multiple Sclerosis Registry: a 50-year follow-up." Multiple Sclerosis 5(4): 293-296.
Trojano, M. (2004). "Can databasing optimise patient care?" Journal of Neurology 251 Suppl 5: v79-v82

Natural history cohorts: we have undertaken this search in order to identify any natural history cohorts on people who have been diagnosed with clinically isolated syndrome.

Search strategy

Medline (Ovid), searched 15/06/2016

Ovid MEDLINE(R) 1946 to June Week 1 2016

1.	Demyelinating Diseases/	10651
2.	Myelitis, Transverse/	1188
3.	exp Optic Neuritis/	6937
4.	Encephalomyelitis, Acute Disseminated/	1743
5.	Demyelinating Autoimmune Diseases, CNS/	334
6.	demyelinating disease*.tw.	4890
7.	transverse myelitis.tw.	1406
8.	neuromyelitis optica.tw.	1863
9.	optic neuritis.tw.	3891
10.	acute disseminated encephalomyelitis.tw.	1149
11.	devic.tw.	108
12.	ADEM.tw.	610
13.	demyelinating disorder.tw.	352
14.	clinically isolated syndrome.tw.	684
15.	first demyelinating event.tw.	71
16.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	25242
17.	exp Registries/	68513
18.	(registry or registries).tw.	70985
19.	(register or registers).tw.	46371
20.	17 or 18 or 19	141663

21.	exp Cohort Studies/	1554538
22.	(cohort adj (study or studies)).tw.	102915
23.	cohort analy$.tw.	4303
24.	(follow up adj (study or studies)).tw.	39204
25.	21 or 22 or 23 or 24	1585425
26.	16 and 20	85
27.	16 and 25	2328
28.	natural history.tw.	36960
29.	natural course.tw.	6144
30.	untreated.tw.	135224
31.	(("no" or "not") adj2 (treat* or therap*)).tw.	163332
32.	(natural adj2 (progression or development)).tw.	2055
33.	28 or 29 or 30 or 31 or 32	332054
34.	16 and 25 and 33	99
35.	exp Multiple Sclerosis/	48381
36.	multiple sclerosis.tw.	51775
37.	35 or 36	59297
38.	25 and 33 and 37	414
39.	Multiple Sclerosis, Relapsing-Remitting/	4313
40.	relapsing remitting multiple sclerosis.tw.	2275
41.	39 or 40	5120
42.	25 and 33 and 41	133
43.	26 or 34 or 42	302

26 Appendix 8: Details of resource use to derive costs inputs

We document here our calculations for resources used to derive annual unit costs for use in our CIS model.

Table 97: Cost for monitoring people with CIS receiving best supportive care

Resource use	Quantity	Description	Unit costs (£,2015)	Source
MRI	1	RD01A	137.23	NHS reference costs 2014/15[275]
Neurologist visit	1	Outpatient attendance, Neurology 400	175.76	Assumption and consultation with clinical expert (Prof. Olga Ciccarelli, University College London, 2016, personal communication) NHS reference costs 2014/15[275]
MS nurse visit	2	15 minutes	18.75	Assumption and consultation with clinical expert (Prof. Olga Ciccarelli, University College London, 2016, personal communication); Curtis and Burns 2015[260]
Estimated cost for monitoring people with CIS receiving best supportive care				**£350.49**

[1]We assumed a nurse specialist (community) employed on the NHS scale agenda for change Band 6 would require 15 minutes of contact time with a patient receiving disease modifying treatment. £75 per hour of patient-related work (see Table 10.4, p172 in Curtis and Burns 2015[260])

Table 98: Initial cost for monitoring in the first year of commencing DMTs

Resource use	Quantity	Description	Unit costs (£,2015)	Source
Investigations				
Full blood counts	5	DAPS05-haematology	3.01	Assumptions and consultation with clinical expert on the number of FBC, LFTs and renal function tests NHS reference costs 2014/15[275]
Liver function tests	5	DAPS04-clinical biochemistry	1.19	
Thyroid function test	1	DAPS09- Other	7.13	
Renal function tests	5	DAPS04-clinical biochemistry	1.19	
MRI	1	RD01A	137.23	NHS reference costs 2014/15[275]
Neurologist visit	2	Outpatient attendance, Neurology 400	175.76	Assumption and consultation with clinical expert (Prof. Olga Ciccarelli, University College London, 2016, personal communication) NHS reference costs 2014/15[275]
MS nurse visit	2	15 minutes	18.75	Assumption and consultation with clinical expert; Curtis and Burns 2015[260]
Estimated initial cost for monitoring people receiving DMTs (Avonex/plegridy, Betaferon and Copaxone) in first year				**£553.20**
Estimated initial cost for monitoring people receiving Rebif in first year (includes thyroid function test)				**£560.33**

[1]We assumed a nurse specialist (community) employed on the NHS scale agenda for change Band 6 would require 15 minutes of contact time with a patient receiving disease modifying treatment. £75 per hour of patient-related work (see Table 10.4, p172 in Curtis and Burns 2015[260])

Table 99: Subsequent resource use and costs for monitoring DMTs

Resource use	Quantity	Description	Unit costs (£,2015)	Source
Investigations				
Full blood counts	2	DAPS05-haematology	3.01	Assumptions and consultation with clinical expert on the number of FBC, LFTs and renal function tests NHS reference costs 2014/15[275]
Liver function tests	2	DAPS04-clinical biochemistry	1.19	
Renal function tests	2	DAPS04-clinical biochemistry	1.19	
MRI	1	RD01A	137.23	NHS reference costs 2014/15
Neurologist visit	1	Outpatient attendance, Neurology 400	175.76	Assumption and consultation with clinical expert (Prof. Olga Ciccarelli, University College London, 2016, personal communication)
Subsequent annual cost for monitoring people receiving DMTs				**£323.77**

27 Appendix 9: Additional analyses undertaken by the assessment

27.1 *Time-varying model*

In Table 100 the results are presented in terms of cost per QALY for the time varying model. These results showed that the disease modifying strategy was more costly and more effective than best supportive care alone. Disease modifying strategy was approximately £25,400 more costly than best supportive care and produced 1.461 more QALYs, which equated to an ICER of approximately £17,400 per QALY. This indicates that for every additional QALY from disease modifying treatments there is an incremental cost of £17,400.

Table 100: Results based on cost per QALY, time-varying model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
Disease modifying treatments	387,500	25,400	10.125	1.461	17,400
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years;					

SA 2a: Individual drugs from assessment group review, progression confirmed at 3 months and individual drug annualised relapse rate

Results based on the time varying model by individual drug showed that best supportive care was the least costly and least effective strategy (see Table 101). Glatiramer acetate treatment strategy was approximately £26,300 more expensive than the best supportive care treatment strategy and produced 1.105 more QALYs with an ICER of approximately £2700 per QALY. IFN β-1b 250µg every other day (Betaferon) and IFN β-1a 125µg (Plegridy) were both shown to be cost-effective with ICERs of approximately £5700 and £9900 per QALY, respectively. Both IFN β-1a 30 µg IM (Avonex) and IFN β-1a 44 µg SC (Rebif) were dominated by IFN β-1a 125 µg (Plegridy).

Table 101: Results based on the time-varying model, SA 2a

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
Glatiramer acetate 20mg (Copaxone)	388,400	26,300	9.770	1.105	2,700
IFN β-1b 250 µg every other day (Betaferon)	390,500	2100	10.139	0.369	5700
IFNβ-1a 125µg (Plegridy)	395,500	5,000	10.642	0.503	9,900
IFNβ-1a 30µg IM (Avonex)	415,900	20,400	9.994	-0.648	Dominated

SC INFβ-1a 44µg (Rebif)	416,100	20600	10.420	-0.222	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous					

SA 2b: Individual drugs from AG review, progression confirmed at 6 months, and individual drug annualised relapse rate

In Table 102, we report the results based on the time varying model. These results show that IFNβ-1a 125µg (Plegridy) dominated all other disease modifying treatment strategies. When compared to best supportive care, IFN β-1a 125 µg (Plegridy) was more expensive and effective and had an ICER of approximately £3200 per QALY.

Table 102: Results based on the time-varying model, SA 2b

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
IFNβ-1a 125µg (Plegridy)	371,500	9400	11.608	2.944	3200
SC INFβ-1a 44µg (Rebif)	395,700	24,200	11.290	-0.318	Dominated
Glatiramer acetate 20mg (Copaxone)	396,500	25000	9.485	-2.123	Dominated
IM IFNβ-1a 30µg (Avonex)	409,200	37700	10.267	-1.341	Dominated
BSC, best supportive care; IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

27.2 *Incorporating carers' disutilities*

We present analyses below relating to the base run model.

27.2.1 Cost-effectiveness analysis results: base case and sensitivity analyses

Base Case

In Table 103, we present the findings from our base case analysis with the inclusion of carers' disutilities. The results showed that the disease modifying treatment strategy was more costly and more effective than best supportive care. The expected mean costs per person for the disease modifying treatment strategy were approximately £25,700 more costly than the best supportive care strategy and produced 1.046 more QALYs with an ICER of approximately £24,600 per QALY.

Table 103: Base case results based cost per QALY

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)

Best supportive care	362,100	-	7.148	-	-
Disease modifying treatments	387,800	25,700	8.194	1.046	24,600
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

SA 1: Pooled on-scheme DMTs from assessment group review

We used two key estimates of treatment effectiveness from our clinical effectiveness review: the aggregated hazard ratio for disability progression confirmed at 3 months and the aggregated annualised relapse rate.

In Table 104, the results show that disease modifying treatment strategy was more costly and more effective than best supportive care alone. The disease modifying treatment strategy was approximately £10,200 more costly than best supportive care and produced 2.201 more QALYs, which equated to an ICER of approximately £4600 per QALY.

Table 104: Cost per QALY, SA 1

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
Disease modifying treatments	372,300	10,200	9.349	2.201	4600
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

SA 2a Individual drugs from AG review, progression confirmed at 3 months (preferred analysis)

Table 105: Cost per QALY, SA 2a (assessment group estimates of relapse rate and disability progression confirmed at 3 months)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
IFN β-1a 125µg (Plegridy)	379,900	17,800	10.016	2.868	6200
Glatiramer acetate 20mg (Copaxone)	381,000	1100	8.646	-1.552	Dominated
IFN β-1b 250 µg every other day (Betaferon)	393,400	13,500	8.556	-1.46	Dominated
INF β-1a 44µg SC (Rebif)	404,800	24,900	9.614	-0.402	Dominated

IFNβ-1a 30µg IM (Avonex)	406,100	26,200	9.027	-0.989	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

The results in Table 105, were robust to the inclusion of carers' disutilities. These results showed that IFN β-1a 125 µg (Plegridy) remained dominant over all other disease modifying treatment strategies. When compared to best supportive care, IFN β-1a 125 µg (Plegridy) was approximately £17,800 more costly and was more effective by expected mean gains of QALYs, with an ICER of £6200 per QALY.

SA 2b: Individual drugs from AG review, progression confirmed at 6 months

Likewise, these results were robust when we included carers' disutilities in the analysis. Results showed that IFN β-1a 125 µg SC every two weeks (Plegridy) remained dominant over all other strategies included in this analysis (see Table 106).

Table 106: Cost per QALY, SA 2b (assessment group estimates, disability progression confirmed at 6 months)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
IFN β-1a 125 µg SC every two weeks (Plegridy)	347,000	-	11.584	-	-
Best supportive care	362,100	15,100	7.148	-4.436	Dominated
IFN β-1a 44 µg SC three times a week (Rebif)	377,600	30,600	10.966	-0.618	Dominated
Glatiramer acetate 20 mg SC daily (Copaxone)	391,900	44,900	8.236	-3.348	Dominated
IFN β-1a 30 µg IM once weekly (Avonex)	396,900	49,900	9.446	-2.138	Dominated
BSC, best supportive care; IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

SA 3: Hazard ratios from company submissions

When we used the estimates for treatment effectiveness (annualised relapse rate and disability progression) reported by each company and included carers' disutilities, these results showed that IFN β-1a 125 µg (Plegridy) dominated all other disease modifying treatment strategies (see Table 107). When compared to best supportive care, IFN β-1a 125 µg (Plegridy) resulted in an ICER of £3000 per QALY.

Table 107: Cost per QALY, SA 3 (company estimates of effectiveness)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
IFN β-1a 125 µg SC every two weeks (Plegridy)	366,300	4200	8.566	1.418	3000
Glatiramer acetate 40 mg SC three times weekly (Copaxone)	387,000	20,700	7.971	-0.775	Dominated
IFN β-1a 30µg IM once weekly (Avonex)	387,600	21,300	8.149	-0.417	Dominated
IFN β-1a 44µg SC three times a week (Rebif)	412,900	46,600	8.318	-0.248	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

SA 4: Time horizon changed from 50 years to 20 and 30 years

Table 108 and Table 109 show the results based on a 20-year and 30-year time horizon, respectively. Findings showed that the glatiramer acetate treatment strategy continued to be extendedly dominated by IFN β-1a 125 µg (Plegridy) in both analyses, with the inclusion of carers' disutilities. Additionally, IFN β-1a 125 µg (Plegridy) dominated both IFN β-1a 30 µg IM (Avonex) and IFN β-1a 44µg SC (Rebif) treatment strategies. Excluding all dominated strategies, IFN β-1a 125 µg (Plegridy) when compared to best supportive care had an ICER of approximately £ and £ per QALY for the 20-year and 30-year time horizon, respectively.

Table 108: Cost per QALY, SA 3 (time horizon changed to 20 years)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	196,900	-	5.710	-	-
Glatiramer acetate 20mg (Copaxone)	220,500	23,600	6.628	0.918	Extendedly dominated
IFNβ-1a 125µg (Plegridy)	225,800	28,900	7.301	1.591	18,200
IFNβ-1a 30µg IM (Avonex)	242,600	16,800	6.789	-0.512	Dominated
IFN β-1a 44µg SC (Rebif)	245,200	19,400	7.156	-0.145	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous					

Table 109: Cost per QALY, SA 3 (time horizon changed to 30 years)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	279,400	-	6.540	-	-
Glatiramer acetate 20mg (Copaxone)	298,900	19,500	7.790	1.25	Extendedly dominated
IFNβ-1a 125µg (Plegridy)	300,400	21,000	8.809	2.269	9300
INFβ-1a 44µg SC (Rebif)	322,900	22,500	8.551	-0.258	Dominated
IFNβ-1a 30µg IM (Avonex)	323,000	22,600	8.057	-0.752	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous					

28 Appendix 10: Results by age of RRMS onset

Using the base run RSS model, we derived mean costs and mean QALYs for the best supportive care and disease modifying treatments arm, for various ages of onset of relapsing remitting multiple sclerosis.

Table 110: Mean costs and QALYs by age of onset of RRMS

Age	Mean costs (best supportive care) (£)	Mean QALYs (best supportive care)	Mean costs (DMTs) (£)	Mean QALYs (DMTs)
30	362,128	8.664	387,755	9.607
31	360,392	8.643	386,012	9.583
32	358,487	8.620	384,100	9.557
33	356,426	8.596	382,032	9.528
34	354,182	8.569	379,780	9.497
35	351,763	8.540	377,352	9.464
36	349,145	8.508	374,727	9.428
37	346,303	8.474	371,876	9.388
38	343,252	8.437	368,817	9.345
39	339,985	8.397	365,542	9.299
40	336,479	8.354	362,029	9.250
41	332,764	8.309	358,310	9.197
42	328,825	8.261	354,369	9.141
43	324,639	8.208	350,182	9.081
44	320,230	8.153	345,775	9.017
45	315,615	8.095	341,167	8.950
46	310,782	8.034	336,345	8.879
47	305,740	7.969	331,319	8.804
48	300,491	7.901	326,089	8.725
49	295,059	7.829	320,683	8.642
50	289,449	7.754	315,105	8.555
51	283,682	7.677	309,378	8.465
52	277,718	7.595	303,458	8.371
53	271,632	7.511	297,427	8.273
54	265,398	7.423	291,254	8.171
55	259,060	7.333	284,987	8.067
56	252,565	7.239	278,568	7.957
57	245,948	7.141	272,034	7.844
58	239,201	7.040	265,374	7.726
59	232,326	6.934	258,589	7.604
60	225,352	6.825	251,711	7.477
61	218,270	6.712	244,724	7.346
62	211,077	6.595	237,624	7.210
63	203,763	6.472	230,397	7.068
64	196,405	6.345	223,122	6.922
65	189,004	6.216	215,799	6.772
66	181,530	6.081	208,388	6.616
67	174,037	5.942	200,947	6.457
68	166,497	5.798	193,437	6.292
69	158,995	5.652	185,950	6.124
70	151,501	5.501	178,447	5.951
71	144,046	5.347	170,955	5.775
72	136,611	5.187	163,444	5.593
73	129,248	5.024	155,968	5.407
74	121,999	4.858	148,568	5.219
75	114,851	4.688	141,220	5.027

Age	Mean costs (best supportive care) (£)	Mean QALYs (best supportive care)	Mean costs (DMTs) (£)	Mean QALYs (DMTs)
76	107,837	4.515	133,956	4.833
77	101,019	4.342	126,843	4.637
78	94,362	4.165	119,833	4.440
79	87,944	3.989	113,014	4.243
80	81,775	3.814	106,399	4.048

Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence. ADDENDUM

Title: Clinical and cost-effectiveness of beta interferon and glatiramer acetate for treating multiple sclerosis – ADDENDUM WITH NON-CONFIDENTIAL ANALYSES

Produced by: Warwick Evidence

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Declared competing interests of the authors

Prof. Olga Ciccarelli received consultancy fees from Novartis, Biogen-Idec and General-Electric, Genzyme (*) All payments were made to her employer, UCL Institute of Neurology. She also received reimbursement for attending a symposium from Novartis and ECTRIMS, and funds for research from the UK MS Society, EPSRC, UCLH and BRC

Professor Aileen Clarke is an editor of the journal: Health Technology Assessment. All payments are made to her employer. Warwick Medical School

Prof. Carl Counsell received funding through Biogen-Idec, who provided some funding for a departmental MS nurse. Prof. Carl Counsell has also authored a paper that was critical of the UK Risk Sharing Scheme for disease modifying therapies in MS (Sudlow, CLM, Counsell, CE. Problems with UK government's risk sharing scheme for assessing drugs for multiple sclerosis. BMJ 2003; 326:388-392.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

All CIC (Commercial in Confidence) data has been highlighted in blue and underlined, all AIC (Academic in Confidence) data is highlighted yellow and underlined

This report should be referenced as follows:

Contributions of authors

GJMT coordinated the project, led the review of clinical effectiveness and led the drafting of the report. PA led the review of cost effectiveness, the critique of the RSS submission and the economic modelling and contributed to drafting the report. XA co-led the review of clinical effectiveness and contributed to the drafting of the report. HM and JM contributed to the economic evaluation work and contributed to drafting the report. RC contributed

to the reviews of clinical and cost effectiveness through search and information specialist support and to the drafting of the report. AK and SL contributed to the review of clinical effectiveness and to the drafting of the report. CC and OC contributed as clinical experts and to the drafting of the report. JP and JR contributed to the review of clinical effectiveness and to the drafting of the report. HF contributed to drafting the report. AC supervised the project and contributed to the drafting of the report.

Please refer to the International Committee of Medical Journal Editors (ICMJE) ***Uniform Requirements for Manuscripts Submitted to Biomedical Journals see*** http://www.icmje.org/

Multiway sensitivity analyses were undertaken, and these are summarised below:

1. **SA 1 Pooled on-scheme DMTs from assessment group review.** In this analysis, we used inputs from our review of the evidence pooled across all on-scheme DMTs. We used the aggregated hazard ratio for disability progression confirmed at 3 months, the aggregated annualised relapse rate, and the aggregated discontinuation rate.
   This is as in the original report. However, please see errata as there was a transcription error in the original which has now been corrected.

2. **SA 2 Individual drugs from AG review**
   a. **Individual drugs from AG review, progression confirmed at 3 months.** Using the hazard ratio for disability progression confirmed at 3 months derived from our clinical effectiveness review, with the rate ratio for annualised relapse rate derived from our clinical effectiveness review, as well as relevant discontinuation rates and list prices
      This analysis is as previously presented but we have now included carer's disutilities and present versions with the time-varying model.
   b. **Individual drugs from AG review, progression confirmed at 6 months.** Using the hazard ratio for disability progression confirmed at 6 months derived from our clinical effectiveness review, with the rate ratio on annualised relapse rate derived from our clinical effectiveness review, as well as relevant discontinuation rates and list prices
      This is as in the original report.
3. **SA 3 Hazard ratios from company submissions.** Using the hazard ratios (confirmed disease progression) reported by each company with the annualised relapse rates reported by each company, as well as relevant discontinuation rates and list prices

   This analysis is as previously presented but we have now included carer's disutilities and present versions with the time-varying model.

4. **SA 4 Time horizon changed.** Individual drugs from AG review, progression confirmed at 3 months and relapse rate from clinical effectiveness review, relevant discontinuation rates and list prices, with time horizon changed from 50 years to 20 years or 30 years.
   This is an additional new sensitivity analysis. We also included carer's disutilities and the time-varying model
5. **SA 5 Parameter uncertainty analysis for the base case and SA 1.** We varied the hazard ratio for disability progression, the rate ratio for annualised relapse rates, cost of disease modifying treatments, and the annual discontinuation rate by ±10% for the base case and SA

This analysis is as previously presented but we have now included carer's disutilities and present versions with the time-varying model.

We present here non- confidential analyses.

SA 2 Individual drugs from AG review: Individual drugs from AG review, progression confirmed at 3 months. Using the hazard ratio for disability progression confirmed at 3 months derived from our clinical effectiveness review, with the rate ratio for annualised relapse rate derived from our clinical effectiveness review, as well as relevant discontinuation rates and list prices. An additional analysis using discounted prices is presented in a separate addendum.

Table 1: Cost per QALY, SA 2a (using the base run model and including carers' disutilities)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
IFN β-1a 125 µg SC every two weeks (Plegridy)	379,900	17,800	10.016	2.868	6200
Glatiramer acetate 20 mg SC daily (Copaxone)	381,200	1300	8.645	-1.371	Dominated
IFN β-1b 250 µg every other day (Betaferon)	393,400	13,500	8.556	-1.46	Dominated
IFN β-1a 44µg SC three times a week (Rebif)	394,200	14,300	9.614	-0.402	Dominated
IFN β-1a 30µg IM once weekly (Avonex)	406,400	26,500	9.025	-0.991	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

Table 2: Cost per QALY, SA 2a (using the base run time-varying treatment effect and excluding carers' disutilities)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
Glatiramer acetate 20 mg SC daily (Copaxone)	388,600	26,500	9.769	1.105	Extendedly dominated
IFN β-1a 125 µg SC every two weeks (Plegridy)	395,500	33,400	10.642	1.978	16,900
IFN β-1b 250 µg every other day (Betaferon)	400,300	4800	9.698	-0.944	Dominated

IFN β-1a 44µg SC three times a week (Rebif)	406,000	10,500	10.420	-0.222	Dominated
IFN β-1a 30µg IM once weekly (Avonex)	415,900	20,400	9.994	-0.648	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

Table 3: Cost per QALY, SA 2a (using the base run with time-varying treatment effect and including carers' disutilities)

Strategy	**Mean cost (£)**	**Incremental costs (£)**	**Mean QALYs**	**Incremental QALYs**	**ICER (£)**
Best supportive care	362,100	-	7.148	-	-
Glatiramer acetate 20 mg SC daily (Copaxone)	388,600	26,500	8.371	1.223	Extendedly dominated
IFN β-1a 125 µg SC every two weeks (Plegridy)	395,500	33,400	9.354	2.206	15,100
IFN β-1b 250 µg every other day (Betaferon)	400,300	4800	8.292	-1.062	Dominated
IFN β-1a 44µg SC three times a week (Rebif)	406,000	10,500	9.107	-0.247	Dominated
IFN β-1a 30µg IM once weekly (Avonex)	415,900	20,400	8.626	-0.728	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

Table 4: SA 3 using the base run model and including carers' disutilities

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
IFN β-1a 125 µg SC every two weeks (Plegridy)	366,300	4200	8.566	1.418	3000
Glatiramer acetate 20 mg SC daily (Copaxone)	374,600	8300	8.432	-0.134	Dominated
IFN β-1a 30µg IM once weekly (Avonex)	387,600	21,300	8.149	-0.417	Dominated
IFN β-1a 44µg SC three times a week (Rebif)	405,200	38,900	8.318	-0.248	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

Table 5: SA 3 using the base run with time-varying treatment effects and excluding carers' disutilities

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
IFN β-1a 125 µg SC every two weeks (Plegridy)	369,900	7800	9.818	1.154	6800
Glatiramer acetate 20 mg SC daily (Copaxone)	379,900	10,000	9.654	-0.164	Dominated
IFN β-1a 30µg IM once weekly (Avonex)	390,600	20,700	9.467	-0.351	Dominated
IFN β-1a 44µg SC three times a week (Rebif)	409,500	39,600	9.570	-0.248	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

Table 6: SA 3 using the base run with time-varying treatment effects and including carers' disutilities

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
IFN β-1a 125 µg SC every two weeks (Plegridy)	369,900	7800	8.438	1.290	6000
Glatiramer acetate 20 mg SC daily (Copaxone)	379,900	10,000	8.246	-0.192	Dominated
IFN β-1a 30µg IM once weekly (Avonex)	390,600	20,700	8.041	-0.397	Dominated
IFN β-1a 44µg SC three times a week (Rebif)	409,500	39,600	8.152	-0.286	Dominated

IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous

SA 4 Time horizon changed. Individual drugs from AG review, progression confirmed at 3 months and relapse rate from clinical effectiveness review, relevant discontinuation rates and list prices, with time horizon changed from 50 years to 20 years or 30 years.

Table 7: SA 4 using the base run model with time-varying treatment effects and including utility values (20-year time horizon)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	196,900	-	5.710	-	-
Glatiramer acetate 20 mg SC daily (Copaxone)	223,000	26,100	6.552	0.842	Extendedly dominated
IFN β-1a 125 µg SC every two weeks (Plegridy)	229,800	32,900	7.150	1.44	22,800
IFN β-1b 250 µg every other day (Betaferon)	232,800	3000	6.492	-0.658	Dominated
IFN β-1a 44µg SC three times a week (Rebif)	239,700	9900	7.030	-0.12	Dominated
IFN β-1a 30µg IM once weekly (Avonex)	245,700	15,900	6.689	-0.461	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

Table 8: SA 4 using the base run with time-varying treatment effects and including utility values (30-year time horizon)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	279,400	-	6.540	-	-
Glatiramer acetate 20 mg SC daily (Copaxone)	304,500	25,100	7.614	1.074	Extendedly dominated
IFN β-1a 125 µg SC every two weeks (Plegridy)	310,400	31,000	8.425	1.885	16,400
IFN β-1b 250 µg every other day (Betaferon)	315,600	5200	7.541	-0.884	Dominated
IFN β-1a 44µg SC three times a week (Rebif)	320,900	10,500	8.242	-0.183	Dominated

IFN β-1a 30µg IM once weekly (Avonex)	329,900	19,500	7.813	-0.612	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

Interpretation

SA1-4 all demonstrate that IFN β-1a 125 µg SC every two weeks (Plegridy) is the dominating option.

SA 5 Parameter uncertainty analysis for the base case and SA 1 (including carers' disutilities).
We varied the hazard ratio for disability progression, the rate ratio for annualised relapse rates, cost of disease modifying treatments, and the annual discontinuation rate by ±10% for the base case and SA1.

Figure 1: Using the base run model and including carers' disutilities

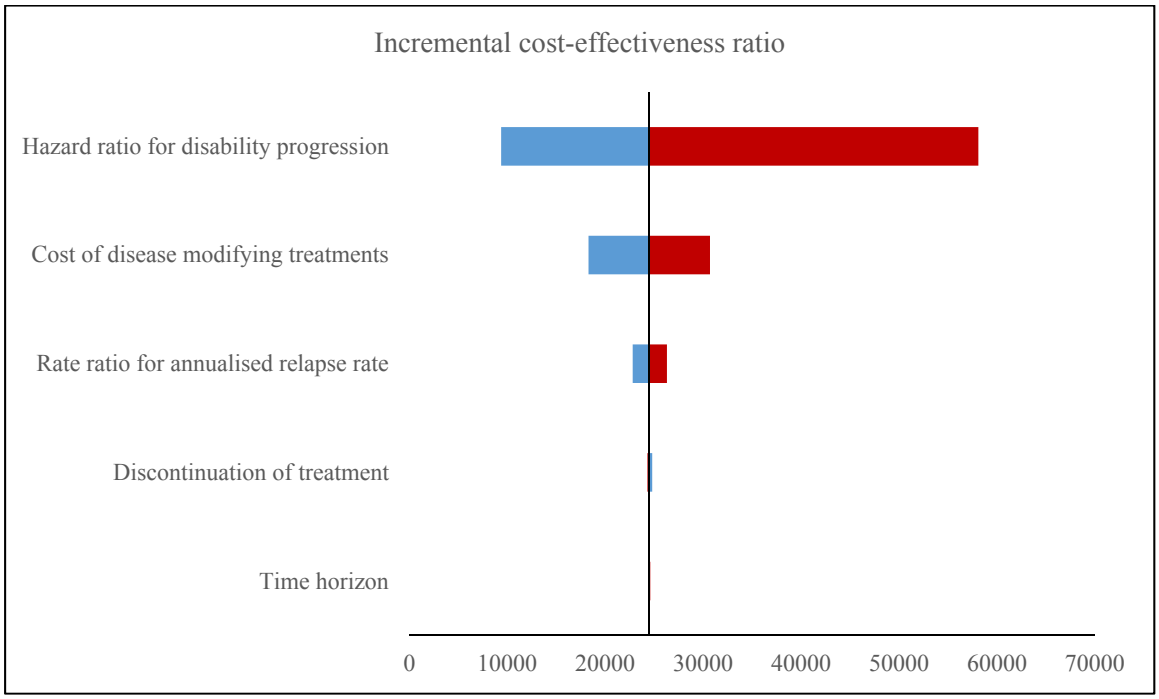


Figure 2: Using the base run model and including carers' disutilities (SA1)

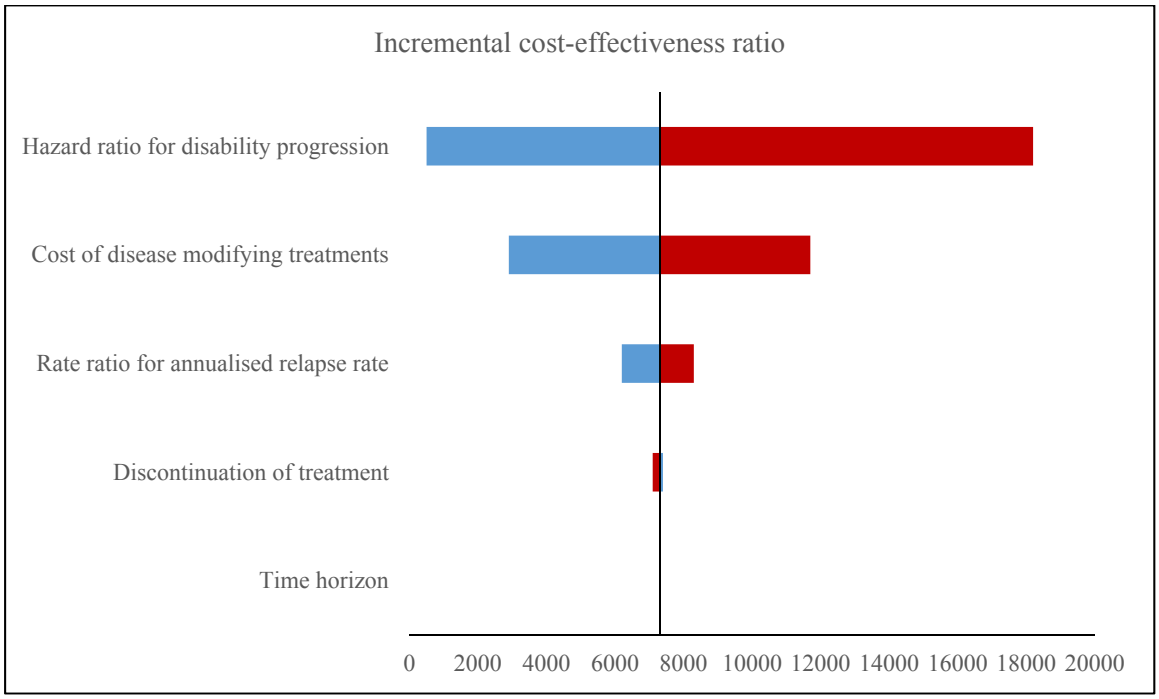


Figure 3: Using the time-varying model and including carers' disutilities

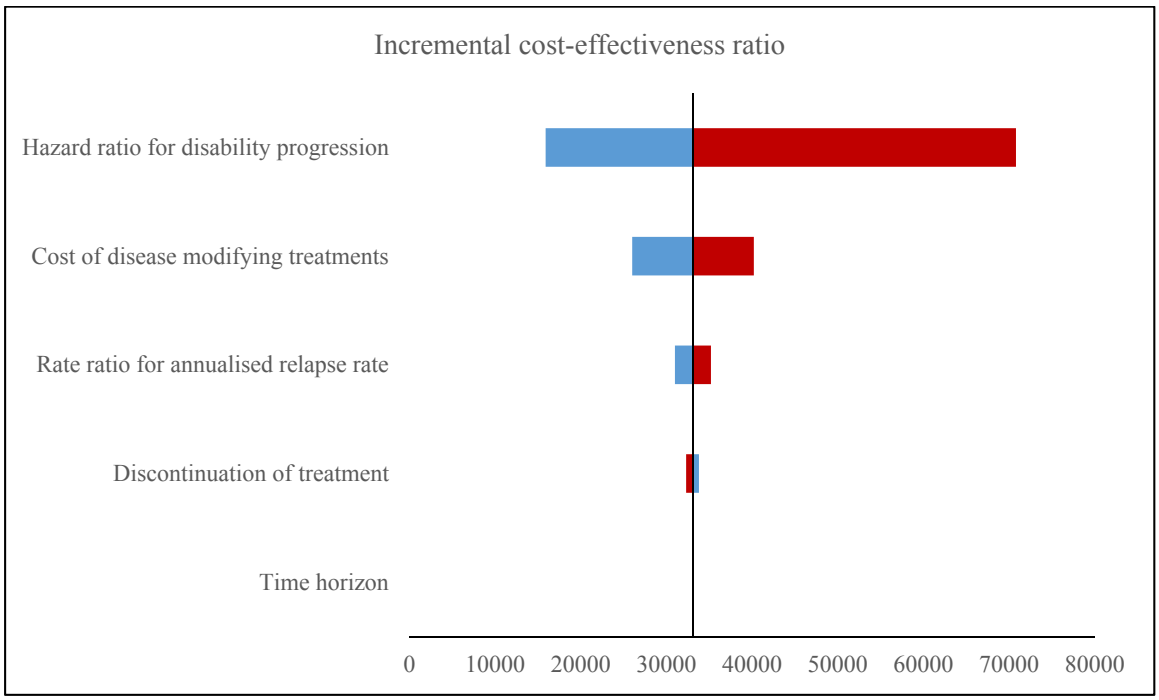
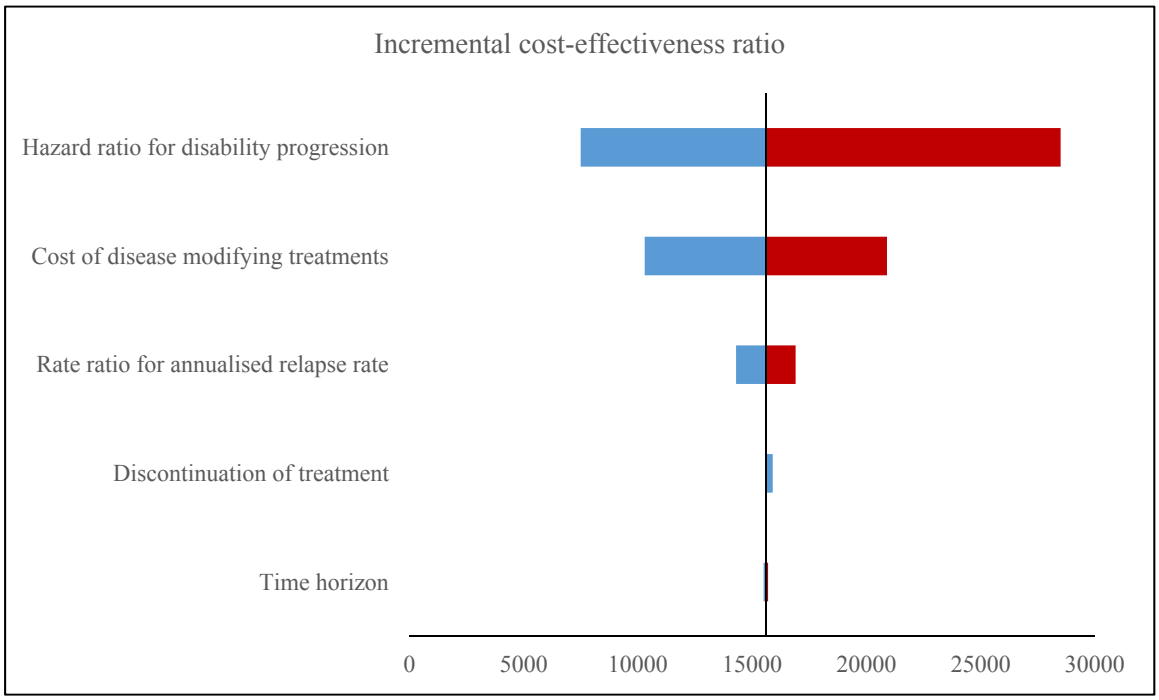


Figure 4: Using the time-varying model and including carers' disutilities (SA1)



Interpretation

SA5 shows that the hazard ratio for disability progression is the factor which has the greatest impact on ICERS regardless of carers' disutility inclusion or use of the time varying model.

SA 6A **Pooled on-scheme DMTs from assessment group review.** In this analysis, we used inputs from our review of the evidence pooled across all on-scheme DMTs. We used the aggregated hazard ratio for disability progression confirmed at 3 months, the aggregated annualised relapse rate, and the aggregated discontinuation rate and individual drug costs.

This analysis is new and uses pooled / aggregated on –scheme DMT effectiveness measures and is presented with or without carer's disutilities and also presents versions with the time-varying model.

Table 9: SA6A using the base run model and including carers' disutilities

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
Glatiramer acetate 20 mg SC daily (Copaxone)	369,600	7500	9.179	2.031	3700
IFN β-1b 250 µg every other day (Betaferon)	376,400	6800	9.179	0.000	Dominated
IFN β-1a 30µg IM once weekly (Avonex)	391,500	21,900	9.179	0.000	Dominated
IFN β-1a 44µg SC three times a week (Rebif)	406,200	36,600	9.179	0.000	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

Table 10: SA6A using the base run model and excluding carers' disutilities

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
Glatiramer acetate 20 mg SC daily (Copaxone)	369,600	7500	10.486	1.822	4100
IFN β-1b 250 µg every other day (Betaferon)	376,400	6800	10.486	0.000	Dominated
IFN β-1a 30µg IM once weekly (Avonex)	391,500	21,900	10.486	0.000	Dominated
IFN β-1a 44µg SC three times a week (Rebif)	406,200	36,600	10.486	0.000	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

Table 11: SA6A using the base run with time-varying treatment effects and including carers' disutilities

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
Glatiramer acetate 20 mg SC daily (Copaxone)	380,400	18,300	8.771	1.623	11,300
IFN β-1b 250 µg every other day (Betaferon)	387,000	6600	8.771	0.000	Dominated
IFN β-1a 30µg IM once weekly (Avonex)	401,600	21,200	8.771	0.000	Dominated
IFN β-1a 44µg SC three times a week (Rebif)	415,800	35,400	8.771	0.000	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

Table 12: SA6A using the base run with time-varying treatment effects and excluding carers' disutilities

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
Glatiramer acetate 20 mg SC daily (Copaxone)	380,400	18,300	10.125	1.461	12,500
IFN β-1b 250 µg every other day (Betaferon)	387,000	6600	10.125	0.000	Dominated
IFN β-1a 30µg IM once weekly (Avonex)	401,600	21,200	10.125	0.000	Dominated
IFN β-1a 44µg SC three times a week (Rebif)	415,800	35,400	10.125	0.000	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

Interpretation

We found that all other options included in the RSS are dominated by Glatiramer acetate 20 mg SC daily (Copaxone) regardless of carers' disutility inclusion or use of the time varying model.

SA 6B **Pooled on-scheme DMTs from assessment group review and discounts and infrastructural contributions.** In this analysis, we used inputs from our review of the evidence pooled across all on-scheme DMTs. We used the aggregated hazard ratio for disability progression confirmed at 3 months, the aggregated annualised relapse rate, and the aggregated discontinuation rate and individual drug costs.

This analysis is new and includes discounts and infrastructural contributions, with or without carer's disutilities and presents versions with the time varying model. ***This analyses will be presented in a separate addendum****.*

Probabilistic sensitivity analyses

PSA Addendum 1

This new PSA includes carer's disutilities. Figures 5, 6 and 7 are on the base run model.

Figure 5 Cost-effectiveness plane, probabilistic sensitivity analysis conducted on base run model and including carers' disutilities

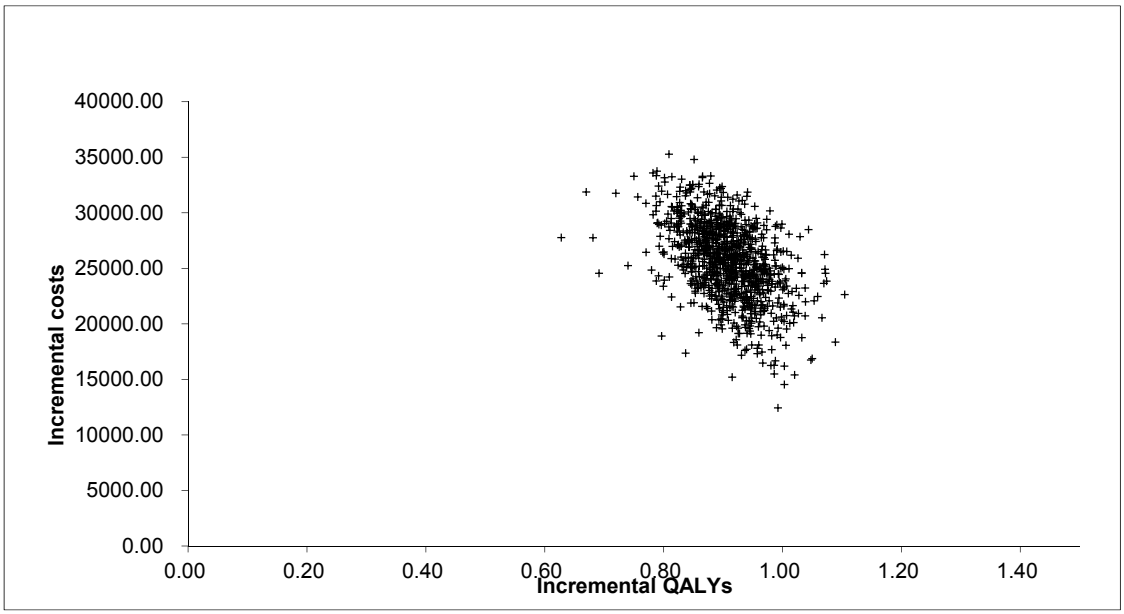
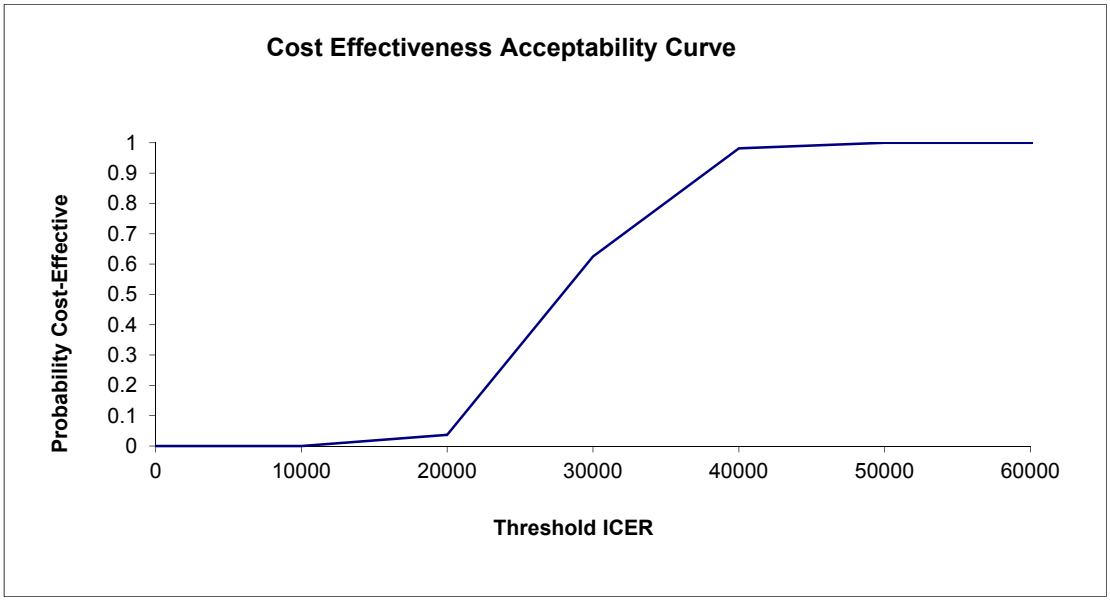


Figure 6 Cost-effectiveness acceptability curve, probabilistic sensitivity analysis conducted on base run model and including carers' disutilities



Interpretation Figures 5 and 6 here suggest that the addition of carers' disutilities makes little difference to our findings as compared to Figure 28 and Figure 29 of our main report.

PSA Addendum 2

This new PSA also includes carer's disutilities Figures 7 and 8 conducted on SA1

Figure 7 Cost-effectiveness plane, probabilistic sensitivity analysis conducted on SA1 and including carers' disutilities

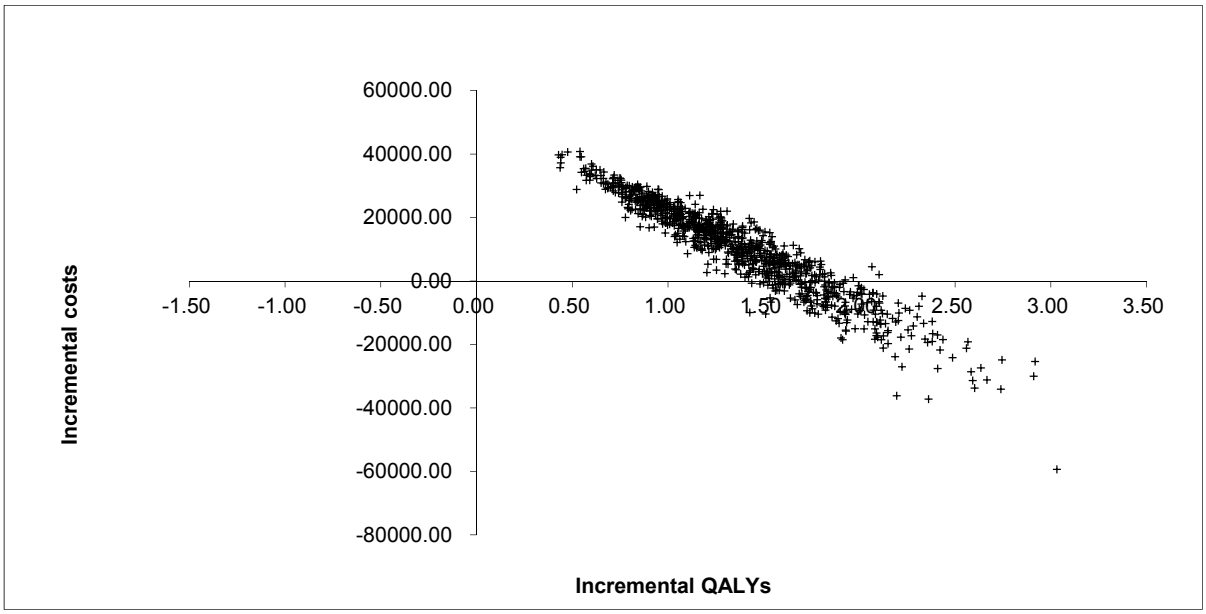
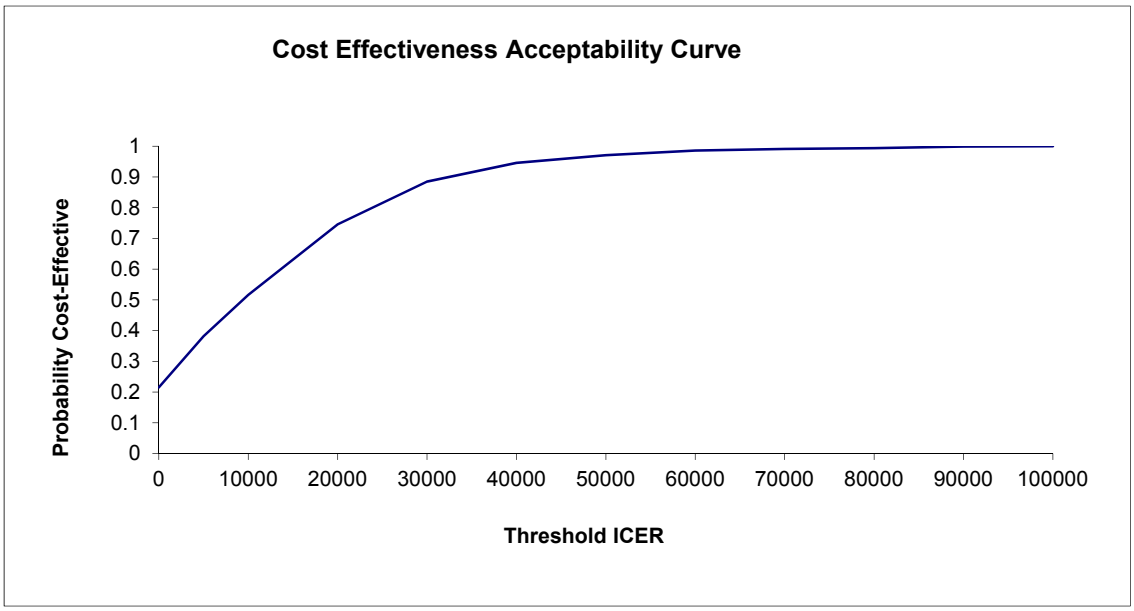


Figure 8 Cost-effectiveness acceptability curve, probabilistic sensitivity analysis conducted on SA1 and including carers' disutilities



Interpretation

Figures 7 and 8 here suggest that the addition of carers' disutilities in SA1 makes little difference to our findings as compared to Figure 30 and Figure 31 of our main report.

PSA Addendum 3

This new PSA includes carer's disutilities. Figures 9 and 10 are on the time-varying model.

Figure 9 Cost-effectiveness plane, probabilistic sensitivity analysis conducted on base run with time varying treatment effects and including carers' disutilities

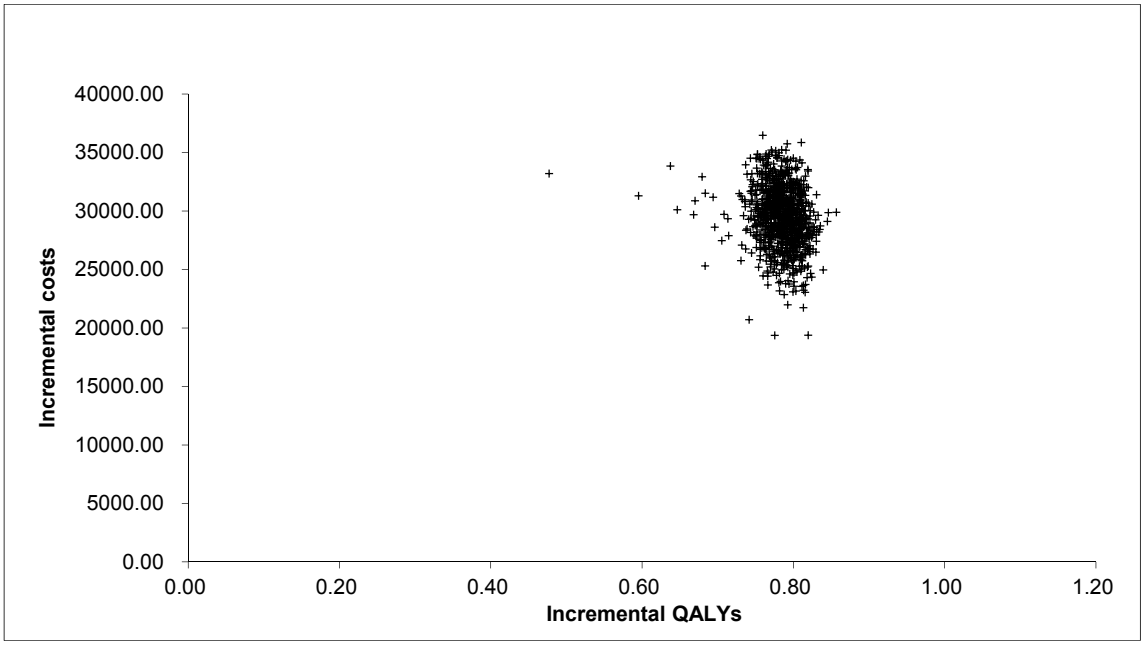
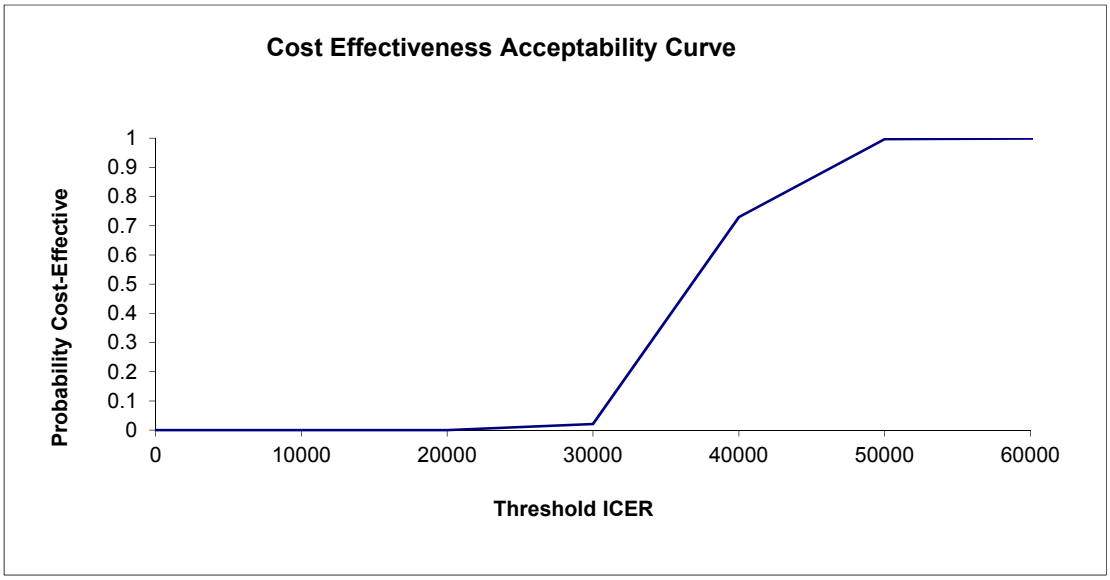


Figure 10 Cost-effectiveness acceptability curve, probabilistic sensitivity analysis conducted on base run with time varying treatment effects and including carers' disutilities



Interpretation

Figures 9 and 10 show that with the time-varying model both incremental QALYs and costs are increased so that the ICER is increased as might be expected. (Compare to Figures 5 and 6).

PSA Addendum 4

This new PSA again includes carer's disutilities. Figures11 and 12 are on SA1 with the time varying model and including carers' disutilities.

Figure 11 Cost-effectiveness plane, probabilistic sensitivity analysis conducted on base run with time varying treatment effects (SA1) and including carers' disutilities

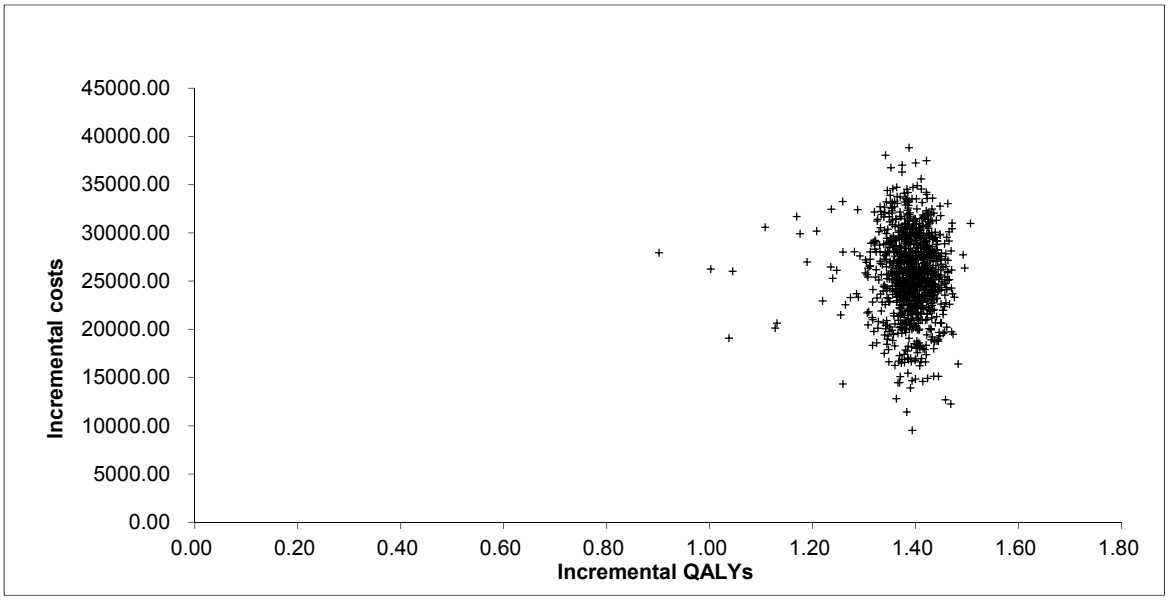
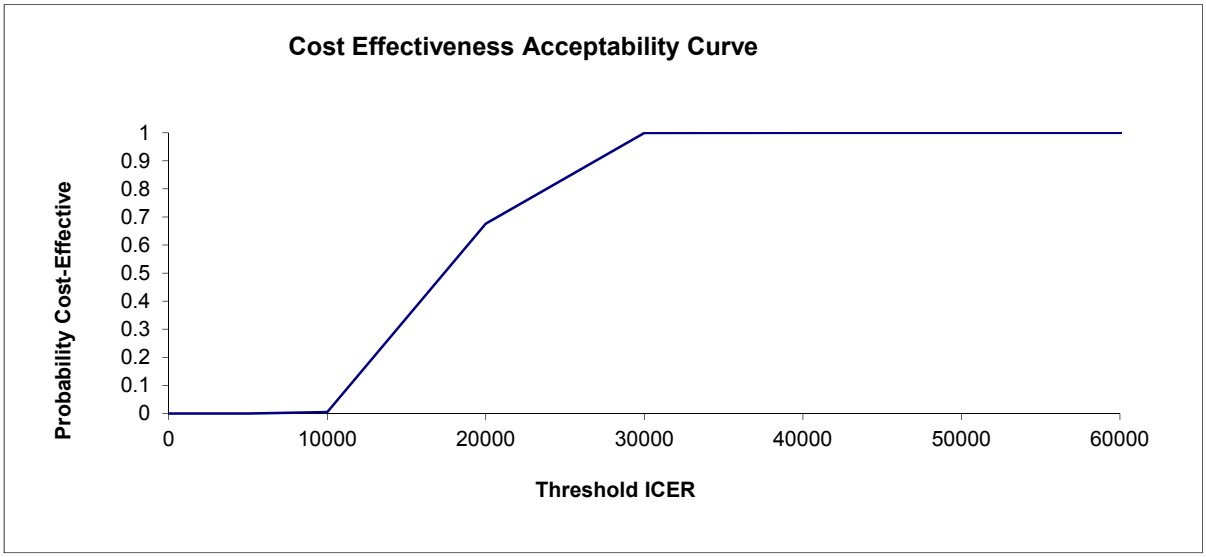


Figure 12 Cost-effectiveness acceptability curve, probabilistic sensitivity analysis conducted on base run with time varying treatment effects (SA1) and including carers' disutilities



Interpretation

Figures 11 and 12 show that the time-varying model increases the ICER.

Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence.

Erratum for Clinical and cost-effectiveness of beta interferon and glatiramer acetate for treating multiple sclerosis

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Declared competing interests of the authors

Prof. Olga Ciccarelli received consultancy fees from Novartis, Biogen-Idec and General-Electric, Genzyme (*) All payments were made to her employer, UCL Institute of Neurology. She also received reimbursement for attending a symposium from Novartis and ECTRIMS, and funds for research from the UK MS Society, EPSRC, UCLH and BRC

Professor Aileen Clarke is an editor of the journal: Health Technology Assessment. All payments are made to her employer. Warwick Medical School

Prof. Carl Counsell received funding through Biogen-Idec, who provided some funding for a departmental MS nurse. Prof. Carl Counsell has also authored a paper that was critical of the UK Risk Sharing Scheme for disease modifying therapies in MS (Sudlow, CLM, Counsell, CE. Problems with UK government's risk sharing scheme for assessing drugs for multiple sclerosis. BMJ 2003; 326:388-392.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Contributions of authors

GJMT coordinated the project, led the review of clinical effectiveness and led the drafting of the report. PA led the review of cost effectiveness, the critique of the RSS submission and the economic modelling and contributed to drafting the report. XA co-led the review of clinical effectiveness and contributed to the drafting of the report. HM and JM contributed to the economic evaluation work and contributed to drafting the report. RC contributed to the reviews of clinical and cost effectiveness through search and information specialist support and to the drafting of the report. AK and SL contributed to the review of clinical effectiveness and to the drafting of the report. CC and OC contributed as clinical experts and to the drafting of the report. JP and JR contributed to the review of clinical effectiveness and to the drafting of the report. HF contributed to drafting the report. AC supervised the project and contributed to the drafting of the report.

Please refer to the International Committee of Medical Journal Editors (ICMJE) ***Uniform Requirements for Manuscripts Submitted to Biomedical Journals see*** *http://www.icmje.org/*

Glatiramer acetate 20 mg SC daily (Copaxone)	391,800	14,200	9.650	-2.391	Dominated
IFN β-1a 30 µg IM once weekly (Avonex)	397,200	5400	10.717	1.067	Dominated
BSC, best supportive care; IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

SA 3: Hazard ratios from company submissions

When we used the estimates for treatment effectiveness (annualised relapse rate and disability progression) reported by each company, results from this sensitivity analysis showed that best supportive care was the least expensive strategy and IFN β-1a 44µg SC three times a week (Rebif) was the most expensive (see Table 75). In terms of QALYs, best supportive care is expected to result in the least QALYs (8.664) and IFN β-1a 125 µg SC every two weeks (Plegridy) expected to yield the most QALYs (9.931). Results also showed that IFN β-1a 125 µg (Plegridy) dominated all other disease modifying treatment strategies. When compared to best supportive care, IFN β-1a 125 µg (Plegridy) demonstrated an ICER of £3300 per QALY.

Table 75: Cost per QALY, SA 3 (company estimates of effectiveness)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
IFN β-1a 125 µg SC every two weeks (Plegridy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg SC daily (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 30µg IM once weekly (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44µg SC three times a week (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

SA 4: Time horizon changed from 50 years to 20 and 30 years

Table 76 and Table 77 show the results based on a 20-year and 30-year time horizon, respectively. These results showed that the glatiramer acetate treatment strategy is extendedly dominated by IFN β-1a 125 µg (Plegridy) in both analyses. Additionally, IFN β-1a 125 µg (Plegridy) dominated both IFN β-1a 30 µg IM (Avonex) and IFN β-1a 44µg SC (Rebif) treatment strategies. Excluding all dominated strategies, IFN β-1a 125 µg (Plegridy) when

Figure 28: Cost-effectiveness plane, probabilistic sensitivity analysis conducted on the base case

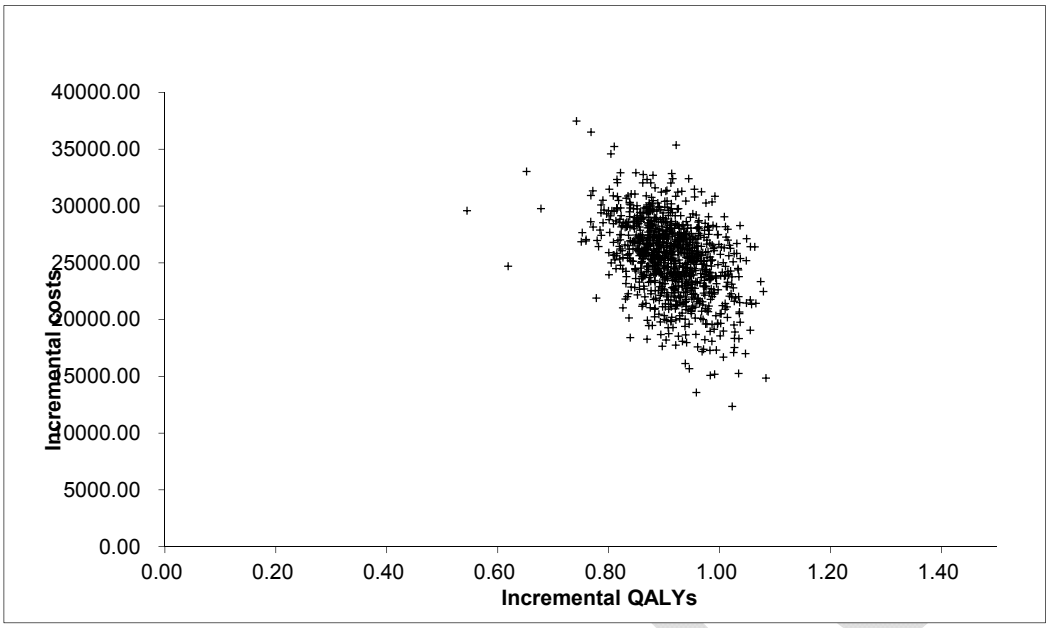
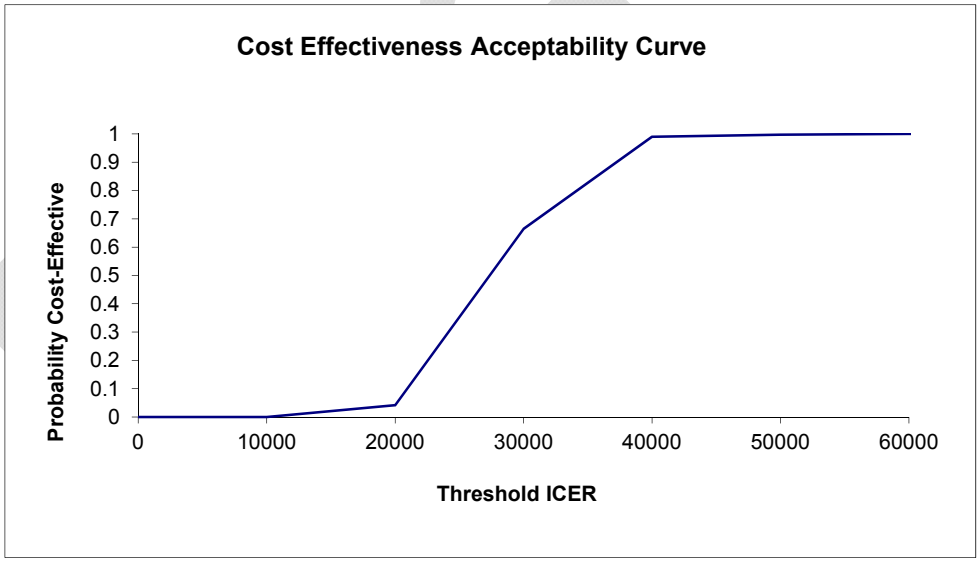


Figure 29: Cost-effectiveness acceptability curve, probabilistic sensitivity analysis conducted on the base case



Probabilistic sensitivity analysis conducted on SA 1

Table 79 presents the results of the probabilistic sensitivity analysis when the findings from the assessment group review were used to estimate the pooled hazard ratio for disability progression and the pooled rate ratio for annualised relapse rates. The probabilistic sensitivity analysis shows that the ICER for disease modifying treatments compared to best supportive care was approximately £8000 per QALY gained.

Table 79: Findings from the probabilistic sensitivity analysis conducted on SA 1

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)

Figure 30: Cost-effectiveness plane, probabilistic sensitivity analysis conducted on SA 1

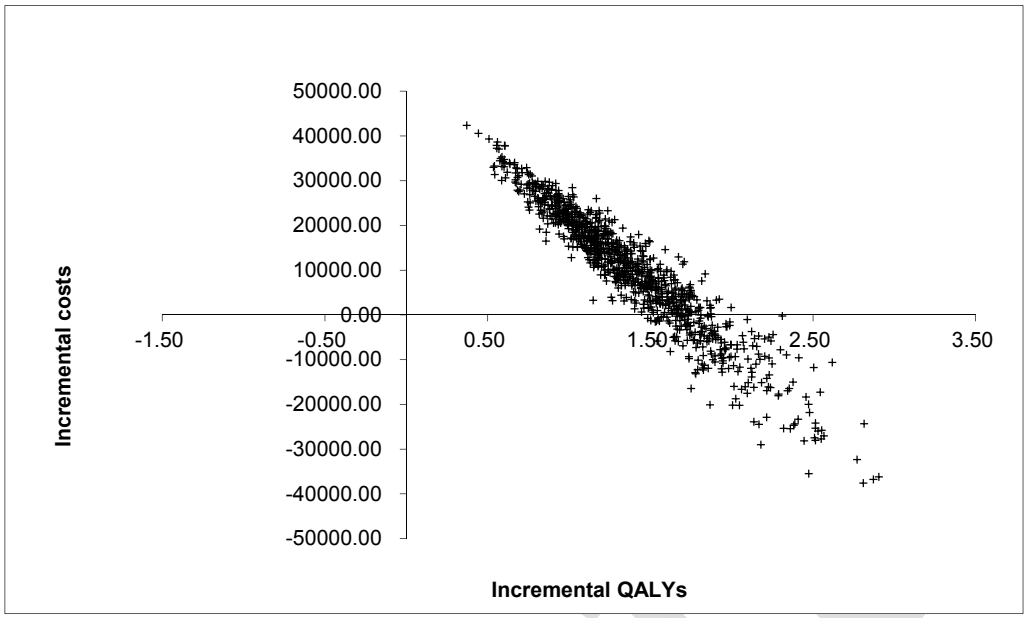
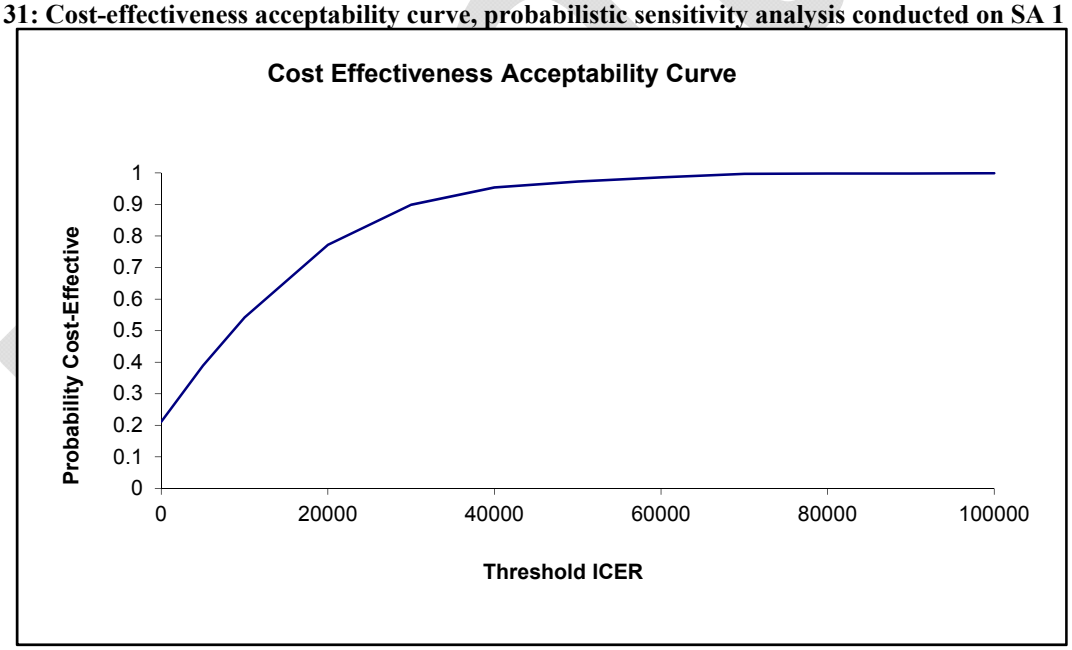


Figure 31: Cost-effectiveness acceptability curve, probabilistic sensitivity analysis conducted on SA 1



Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]

Comments from Biogen on the Assessment Group's Report

On review of the AG report, this document aims to provide Biogen's comments and feedback. Biogen would like to thank NICE for the opportunity to comment.

1. Neutralising Antibodies

In section 5.3.1 (page 39) it is stated "given the biological nature of recombinant IFN-β, patients are at risk of developing neutralising antibodies (NABs) against IFN-β. NABs are thought to increase relapse rates and the rate of disease progression." This statement is not factually correct; there is no evidence to suggest NABs alter the underlying MS disease course. Rather, NABs are thought to reduce the effectiveness of DMTs which may subsequently increase relapse rates and disease progression (as correctly stated in section 6.1 [page 51]).

2. Carer disutilities

Carer disutilities were not included in base case analyses run by the AG. Given the chronic nature of the disease and the impact of the disease on individuals other than the patient due to care needs, Biogen believes it is appropriate to include carer disulitlites in the base case. Furthermore, the NICE reference case does not suggest that carer disutilities should be remove from base case analyses when inclusion of these may be appropriate. The NICE methods guide (Guide to the methods of technology appraisal https://www.nice.org.uk/process/pmg9/chapter/1-foreword) states (Section 5.1.7, page 34): "All direct health effects, whether for patients or, when relevant, carers". The NICE methods guide also states (Section 2.2.8, page 18): "As far as is possible, the scope identifies principal measures of health outcome(s) that will be relevant for the estimation of clinical effectiveness. That is, they measure health benefits and adverse effects that are important to patients and/ or their carers. The clinical outcome measures usually quantify an impact on survival or health-related quality of life that translates into quality-adjusted life years (QALYs) for the evaluation of cost effectiveness". It should also be noted that all previous submissions have included caregiver disutilities and this has been accepted.

3. Transition probabilities: disease progression, relapse and mortality

In Section 14.4.7 (page 256) it is stated: "Whilst it may be difficult to argue which of the London Ontario or British Columbia data sets provide the optimal representation of disease progression in MS patients not receiving DMTs, it would seem unorthodox to use patients recruited into the placebo arm of a clinical trial to represent this". For accuracy and context, Biogen requests that it be acknowledged that this has been standard practice in all recent Single Technology Appraisals (STAs) of DMTs, and that this has been accepted by respective ERGs. Furthermore, without use of placebo as an anchor point in the network meta analyses (NMAs) and moreover the assumption it is reflective of BSC (i.e. no treatment), comparative analyses would have been limited, especially for products falling outside of the UK Risk Sharing Scheme (RSS).

In Section 14.4.7 (page 257), it is also stated: “There were significant differences in how treatment waning effect was modelled in the three company submissions. Biogen assumed that there would be no treatment waning effect in their base case analysis, and assumed that the efficacy of DMTs would be maintained”. For accuracy, Biogen requests that it is acknowledged that waning was considered in sensitivity analyses as part of the company’s submission and this actually resulted in negligible impact on results.

4. Use of NHS list prices for DMTs

It is Biogen’s understanding that some DMTs have discounts applied to list prices. [redacted]. In order to represent the true opportunity cost associated with these products and resultant cost-effectiveness, it would be appropriate to include these discounts when analyses are run.

5. Probabilistic sensitivity analyses (PSA)

In a number of PSA iterations, treatment is dominated by best supportive care and reports lower QALYs and higher costs. These scenarios are not clinically plausible or credible given active treatment has been proven to provide a direct clinical benefit to patients and thus higher overall QALYs compared to best supportive care. These results are likely driven by the large confidence intervals surrounding the utility values as taken from the 2001 ScHARR cost-effectiveness model. Due to the extremely wide confidence intervals applied to these utility values, which in Biogen’s view are also clinically as well as statistically implausible the correlation between decreasing utility values and increasing MS severity is lost i.e. a higher utility (improvement in quality of life) will be applied to a more severe EDSS state than the EDSS state preceding it. This contrasts with what is observed in clinical practice and thus probabilistic results need to be placed in a context for appropriate interpretation and validity.

Multiple Technology Appraisal (MTA)

Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]

Merck's comments on Technology Assessment Group Report

On behalf of Merck, please find our comments on the Technology Assessment Group's (TAG) Report, dated 30th August 2016, for Beta interferon and glatiramer acetate for treating multiple sclerosis.

Summary

Merck partially supports the conclusions reflected in the TAG report. We are pleased with the acknowledgement that all the DMTs are cost-effective, as this is consistent with the Risk Share Scheme (RSS) conclusion. The RSS was established to provide patients' access to these DMTs in a manner cost-effective for the NHS. The TAG report, if accepted by the NICE committee, will maintain eligible patient and clinician choice when determining the most suitable therapy.

However, Merck would like to draw particular attention to the following regarding the TAG report:

- The statement that Pegylated IFN β-1a 125 µg is the most cost effective option should be reviewed, due to the issue the TAG itself has raised regarding the uncertainties around their NMA with respect to Pegylated IFN β-1a 125 µg.
- The TAG used Rebif's list price and therefore overstates its acquisition cost, resulting in ICERs for Rebif substantially greater than if the actual cost to the NHS is employed
- It is unclear which hazard ratios (NMA or RSS) from the companies were used for the individual treatment analysis.
- It is unclear how the TAG assessed GA as cost-effective in CIS
- The exclusion of carer utility decrements from the RSS model
- The adaptation of the approach to mortality in the model

1.1. Cannot conclude that Pegylated IFN β-1a 125 µg is 'the most cost-effective option'.

Merck welcomes the main finding of the TAG report, the acceptance of disease modifying therapy as clinically and cost-effective in both RRMS and CIS. We accept that the placebo-controlled studies may reasonably be criticised for their short follow-up, but there is now an abundance of long-term studies on the efficacy of the interferons (interferon ß-1b, interferon ß-1a IM, and interferon ß1a SC) such as PRISMS[1] which provides evidence of long-term evidence for well over a decade.

Merck recognises the difficulties in conducting network meta-analyses in MS, especially the likelihood and impact of heterogeneity. In part this may arise due to the period of time over which evidence has been generated in pivotal and other studies. In the case, of the longer acting interferon Pegylated IFN β-1a 125 µg (PLEGRIDY), the least is known from a placebo controlled study which was performed most recently. It consisted of a very different selected population (relapse rates in the placebo groups of studies into multiple sclerosis have been decreasing since the 1980s[2,3]) and with study duration of just 48 weeks.[4,5]

It is also generally recognised that the earlier in the disease RRMS patients are treated the better the outcome, and in the Pegylated IFN β-1a 125 µg trial patients began treatment at a lower EDSS stage than those incorporated in the original pivotal trials[6] (mean EDSS <2.5, mean duration of disease 6.5 years and less than 10% of patients previously treated.)

There is evidence comparing the interferons with glatiramer acetate through head-to-head studies (BEYOND, REGARD and COMBIRx), but no such comparison is available involving pegylated IFN β-1a 125 µg that can inform the network, and this may be compounded by the factors noted above, (the short study duration and inclusion of patients with less active disease). The TAG report states, in summarising cost-effectiveness results, that Pegylated IFN β-1a 125 µg is the most cost-effective option. Despite the TAG's own misgivings regarding the evidence base for Plegridy, their conclusion is not qualified

"*However, one limitation of the analyses undertaken with data from the NMAs is that they at times relied on sparse networks with uneven risk of bias throughout the network. For example, analyses relating to pegylated IFN β-1a 125 µg (Plegridy) relied on one trial that was not connected to any other trials except by a placebo comparator.* ***Thus, any issues with the estimates derived from our review of clinical effectiveness would have been propagated through the analysis of cost effectiveness***" (p302 TAG report)

This concern is compounded, given the changes in classification of MS between the time of PRISMS (PRISMS 1998 - RRMS by Poser criteria) and other placebo controlled trials of

Interferon Betas and GA, and the single Pegylated IFN β-1a 125 µg study (ADVANCE 2014 - RRMS by 2005 McDonald criteria).

The final point here is that the hazard ratio (HR) for Rebif 44 versus pegylated IFN β-1a 125 µg (TTP3), is reported (p131) as 1.01 (95% confidence interval 0.59, 1.74). Yet despite this, and the other concerns noted above, the TAG's statement that Pegylated IFN β-1a 125 µg was the most the most cost-effective product is presented without any accompanying assessment of uncertainty. No explanation was provided as to why probabilistic sensitivity analysis (PSA) such as that performed for the pooled analysis is absent from the analyses of the individual products.

1.2. The use of Rebif's list price instead of the actual cost to the NHS

In their assessment the TAG used Rebif's list price in its analysis of individual products. Whilst this is an acceptable approach when dealing with products that have 'Commercial in Confidence' prices, it should be pointed out clearly where there is a commercial in confidence agreement with the Department of Health (DH), equivalent to a Patient Access Scheme (PAS), in place for Rebif. The costs associated with Rebif in the TAG's analysis are therefore much greater than under this agreement (such that Rebif's ICER will be overestimated). In the case of Rebif the impact of this on the analyses (including comparison with pegylated IFN β-1a 125 µg) is compounded as the TAG notes (p266),, by their not having 'specifically' taken into account Rebif's marketing authorisation. Patients on Rebif 44 mcg three times per week may (and in many cases do) subsequently have their dosage reduced to 22 mcg three times per week and therefore have lower associated costs. This treatment pattern is not reflected in the TAG's model.

1.3. Lack of clarity on which HRs were used

In the TAG's Sensitivity Analysis 3 (SA3) (p267), the assessment group utilised efficacy data from the company submissions. Here the hazard ratios for confirmed disease progression and rate ratios for annualised relapse that were reported by each company were inputted to the model, as well as relevant discontinuation rates and list prices. It is difficult to understand whether the TAG utilised company NMA, or RSS results in this analysis. This is particularly important, as the validity of the analysis is reduced if RSS results were used for cross-comparison. Results from the RSS for individual products should not be compared with one another (due for example to likely selection bias within the scheme). Additionally, the RSS results for the DMT's should not be compared against estimates for pegylated IFN β-1a 125 µg based on randomised evidence (NMA).

1.4. Lack of clarity on the TAG's CIS model

In the analysis for CIS, Rebif 44mcg is presented as having the lower HR for conversion to MS (0.48), and patients developing MS are treated according to the RRMS analysis (for each drug). In the TAG's RRMS analysis where each treatment is compared individually, Rebif generates a greater QALY outcome than any of the alternatives in the TAG CIS analysis. Given that patients who discontinue in the TAG's CIS model, who subsequently develop MS are then assigned outcomes based on the pooled RRMS analysis, it is unclear how the results in the CIS analysis come about. It would appear that discontinuation is an important driver in the TAG CIS model, particularly given the sensitivity analysis presented by the TAG.

Although the dosage applied for Rebif in CIS is 44mcg, the overall analysis relies on continued treatment following MS conversion. As in the RRMS analysis therefore, the use of list prices, and the failure to recognise the potential for some patients to be managed on 22mcg over the longer term will also impact the CIS analysis, particularly for Rebif.

1.5. Exclusion of carer disutilities

In the main analyses, The TAG evidences the NICE reference case in recognising direct health effects, to the exclusion of any burden falling on informal carers. Caregiver burden in MS is clearly important, and has been incorporated in previous NICE appraisals[7] as well as having been recognised by DH as an appropriate concern to be addressed in the RSS model. The reference case refers to direct health effects, whether for patients or other people. The exclusion of possible health effects on carers of people with MS represents a structural modification of the RSS model.

1.6. Adaptation of approach to mortality

The TAG report notes the possibility of some duplication of mortality effects in the RSS model on which the Merck submission is based, as both a general standardised mortality ratio (SMR) and EDSS specific mortality rates are applied at higher EDSS levels; the former is an RSS assumption whilst the latter derives from the original Sheffield (ScHARR) model, and for which the separately estimated natural history progression probabilities are adjusted. In fact EDSS specific mortality is low at EDSS<8, and the impact on cost-effectiveness analyses of any duplication will principally relate to this as the common SMR applied to all

patients is unaffected by treatment (though will modify overall mortality and therefore actual cost-effectiveness model results). In Merck's sensitivity analyses employing SMRs varied by EDSS, the ScHARR based EDSS specific mortality is set to zero.

Conclusion

Merck agrees with the TAG's affirmation of the RSS analyses, which that found the relevant DMTs in this appraisal to be cost-effective. The TAG reported the MS society's comments that; "*The range of treatment options allows for the differential way MS can affect individuals and their differential responses to DMTs*." We support this principle and encourage approval for all the DMT's being assessed, so that for the patient and clinician, choice is maintained.

References:

[1] Kappos L, Kuhle J, Multanen J, et al. Factors influencing long-term outcomes in relapsing-remitting multiple sclerosis: PRISMS-15. J Neurol Neurosurg Psychiatry 2015; 86(11): 1202-7.

[2] Inusah S, Sormani MP, Cofi eld SS. Assessing changes in relapse rates in multiple sclerosis. Mult Scler 2010; 16: 1414–21.

[3] Palace J, Duddy M, Bregenzer T, Lawton M, Zhu F, Boggild M, et al. Effectiveness and cost-effectiveness of interferon beta and glatiramer acetate in the UK Multiple Sclerosis Risk Sharing Scheme at 6 years: a clinical cohort study with natural history comparator. Lancet Neurol 2015;14:497-505.

[4] Calabresi P et al. ECTRIMS 2013 (P514) http://onlinelibrary.ectrimscongress.eu/ectrims/2013/copenhagen/33994/peter.calabresi.peginterferon.beta-1a.provides.improvements.in.clinical.and.html?history_id=624079

[5] Reuss R. PEGylated interferon beta-1a in the treatment of multiple sclerosis - an update. Biologics. 2013;7:131-8. doi: 10.2147/BTT.S29948

[6] Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol 2014;13:657-65.

[7] Heron Evidence Development. Natalizumab (Tysabri®) for the Treatment of Adults with Highly Active Relapsing Remitting Multiple Sclerosis: Biogen Idec Single Technology Appraisal (STA) Submission to The National Institute for Health and Clinical Excellence. National Institute for Health and Care Excellence; 2007. URL: https://www.nice.org.uk/guidance/TA127/documents/multiple-sclerosis-natalizumab-manufacturer-submissions-biogen-idec-uk-and-elan-pharma-international-ltd-joint-development-agreement-confidential-information-removed2 (Accessed 27/09/2016).

Response to:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

on the Assessment Report for Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]

Prepared by:

Novartis Pharmaceuticals UK Limited

27 September 2016

Dear Sirs,

We would like to thank the National Institute for Health and Care Excellence (NICE) for the opportunity to comment on this Assessment Report. Having reviewed the Assessment Report produced by Warwick Evidence (Assessment Group), Novartis Pharmaceuticals UK Ltd (Novartis) has the following comments and questions:

Page	Text	Novartis questions
60	*"We excluded:"* *"Studies that only examined patients with highly active or rapidly evolving MS, as best supportive care is not an appropriate comparator for these populations"*	Novartis is concerned that the scope of this appraisal has not been clearly defined which may lead to misinterpretation of the guidance following publication. Even though all relevant interventions in the scope of this appraisal (interferon β-1a [Avonex® & Rebif®], interferon β-1b [Betarferon® & Extavia®], pegylated interferon β-1a [Plegridy®], and glatiramer acetate [Copaxone®]) could in theory be used to treat patients with highly active (HA) relapsing remitting multiple sclerosis (RRMS) and patients with rapidly evolving severe (RES) RRMS, it is clear from the exclusion criteria that the Assessment Group interprets the scope for this appraisal to exclude populations with HA RRMS and populations with RES RRMS, because best supportive care is not a relevant comparator in these populations and evidence from studies in these populations has been excluded. Therefore, please could NICE confirm that the assessment report conclusions only apply to first-line treatment of patients with active RRMS? Confusion around the scope is evident from: - the approach to the network meta-analysis conducted by Merck, including interventions/comparators outside the scope (fingolimod [Gilenya®] and natalizumab [Tysabri®] are licensed only in HA and/or RES RRMS) and - the approach to economic analysis conducted by Teva UK Ltd, including interventions/comparators outside the scope (fingolimod [Gilenya®] and natalizumab [Tysabri®] are licensed only in HA and/or RES RRMS). Novartis suggests that the Assessment Report clarifies that the scope excludes HA and RES RRMS and that analyses including treatments for these indications are therefore not relevant.
266	*"Disutilities associated with caring for people with multiple sclerosis were*	Novartis is concerned that the Assessment Group has misinterpreted the reference case and that the approach towards in/exclusion of health effects and costs has been

	included in the RSS analyses. However, it appears that carers included in the analysis represent informal/unpaid carers. The NICE reference case suggests that the perspective should be all direct health effects, whether for patients or other people. Hence, the assessment group has excluded carers' disutilities from the main analysis."	confused. It is stated in the NICE methods guide (2013) that: "For the reference case, the perspective on outcomes should be all direct health effects, whether for patients or other people. The perspective adopted on costs should be that of the NHS and personal and social services." (https://www.nice.org.uk/process/pmg9/chapter/the-reference-case#framework-for-estimating-clinical-and-cost-effectiveness section 5.1.7). Please could NICE confirm that carers' disutilities (representing health effects, not costs) should therefore be included in the base case of the main analysis?
Section 15 & 16	Table 64, 65, 66, 67, 73, and 80 and in text on page 266, 275, and 285	Extavia® appears to be missing from several (but not all) tables and phrases throughout these sections when mentioning Betaferon®. Since they have been considered the same drug in the Assessment Report (page 38, section 5.3.1), could Extavia® please be added to the tables and text when Betaferon® is mentioned?

Novartis would appreciate consideration of these comments and questions and we hope they provide value to the appraisal process.

Yours faithfully,

[redacted]

Teva response to Assessment Group Report

Teva welcomes the Report published by the Assessment Group (AG) and is in agreement with the overall conclusions that Copaxone® and the other disease modifying therapies (DMTs) are cost effective treatments for multiple sclerosis (MS). We do, however, have some concerns regarding the appropriateness of some of the assumptions used by the AG in their modelling. In particular, it appears that a hazard ratio of around 83% is used for Copaxone® when costs *per* QALY were calculated using company estimates of effectiveness (Table 75). However, the "implied hazard ratio" for Copaxone® using the year-10 RSS data, as supplied in our submission (and confirmed by the Department of Health), is [redacted]%, with a similar value also derived from the network meta-analysis (NMA) conducted by Teva. Using these hazard ratios would result in an ICER of approximately £10,000 for Copaxone® as compared to £33,423 in the current Report. Please could the AG explain why they did not use the implied hazard ratio for Copaxone® from the RSS, particularly since it appears that they have used the equivalent ratios for the beta interferons, putting Copaxone® at significant disadvantage in terms of comparative cost effectiveness?

Another major issue related to the modelling is the prominence given to pegylated-interferon beta-1a (Plegridy), particularly in the summary sections of the Report, as the most cost effective treatment for relapsing-remitting MS (RRMS). It is also notable that these results differ greatly to those produced by Biogen Idec (the manufacturer of this product) who presented an ICER value of over £30,000, which is in line with the results for the other interferons. The results for pegylated interferon are based on one trial (ADVANCE)[1] with several recognised and important limitations. The AG acknowledges these limitations, stating on p284 "…*our assessment of Plegridy, in particular, relied on one trial with one year of follow-up…"* and concluded that "…*these limitations led us to believe, on balance, that the RSS was a better choice for the base case*." Disability progression is the key input for the cost effectiveness modelling in MS, and this outcome was only measured as a secondary endpoint after only 48 weeks of therapy in ADVANCE.[1] Guidance from the European Medicines Agency (EMA) in this area states that disability progression should be measured over at least 3 years.[2] Another important caveat of the ADVANCE trial is that this was undertaken many years after the studies for Copaxone® and the other interferons, and represents a significantly different patient population. There is no evidence that pegylated interferon is any more efficacious than the other interferons or Copaxone®; undue emphasis should not be given to this single study, as was recognised in the AG's own main conclusions.

Whilst the Assessment Group acknowledges the limitations of the data available for pegylated interferon, it is disappointing that the main conclusion of the Report, in terms of cost effectiveness in RRMS, appears to place so much emphasis on a single, short-term study. It is also very surprising that the cost effectiveness results for Copaxone® and the (non-pegylated) interferons for RRMS (*e.g.* Table 73) are presented as an incremental analysis and therefore not *versus* best supportive care (BSC), but *versus* pegylated interferon. As *per* the scope, the effectiveness of the DMTs was firstly to be appraised *versus* BSC, and, if appropriate, *versus* each other. To those who do not examine the Report in detail, the way the results are presented gives the entirely misleading impression that most of the DMTs, except pegylated interferon, are being dominated by BSC. The results should be presented as *per* the scope.

Teva strongly recommends that the conclusions drawn in the Report fully reflect the evidence base as a whole and the limitations of the data available, with no undue prominence given to pegylated interferon on the basis of one study. The cost effectiveness results for Copaxone® should also be based on the implied hazard ratio from the RSS ([redacted]%) to ensure a fair comparison *versus* the other DMTs. Overall, we feel that a fairer and more reasonable conclusion is that all the DMTs are cost effective for RRMS.

References

[1] Calabrese P, Kieseier BC, Arnold DL *et al*. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. *Lancet Neurol* 2014; 13: 657–65.
[2] Committee for Medicinal Products for Human Use [CHMP]. Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis. European Medicines Agency, London, 2015. EMA/CHMP/771815/2011, Rev. 2. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500185161.pdf [Accessed September 2016].

Fact Checking of Assessment Group Report

Location	Error/Issue	Correction
p39	Title of Section 5.3.2 is currently "Disease modifying therapies (glatiramer acetate)"	Copaxone® is only drug mentioned in section so change title to "glatiramer acetate" – consistency with section on beta interferons
p39 and p51	"GA is indicated for the treatment of RRMS" "GA is indicated for the treatment of patients with RRMS"	Copaxone® is indicated for "relapsing forms of MS" (SmPC giving details on the populations in which clinical trials have been conducted: 20mg/ml has been studied in RRMS and CIS, 40mg/ml has been studied in RRMS)
p110	Extension of Cop1 MSSG 1995 studied stated to be "up to 11 months"	Blinded extension was this long, but extension study is still ongoing
p110	CONFIRM trial – not stated that Copaxone® was an unblinded reference arm (study used oral placebo)	Limitations of study are noted on p120
p111	Significance for time to relapse in GALA study not stated	"p<0.0001" to be added after "393 days *vs* 377 days"
p128	Copaxone® not included in written listing of NMA results: "Ranking of the drugs suggested…"	Add results for Copaxone®
p164	States that in Teva submission "Dosages were not specified… there is some ambiguity as to whether licensed doses or other dosing regimens included."	All available data (including unlicensed doses) were included in NMA to produce the most robust network possible. Results were presented as *per* the scope (licensed doses only)
p164	Report states that in Teva submission "It appears that both dosages of GA were pooled into one node in the analysis, but this was not clear."	Clearly stated up front in Teva's submission that Copaxone® was presented as a single entity as the dosing regimens are clinically equivalent
p230	Teva's submission is not fully described	Teva provided the DoH approved RSS model with Copaxone® specific data and a *de novo* model to address aspects not covered by the RSS model. Teva requests that this is clarified in the Report
p230	Report states that "…fingolimod, nataliumab and dimethyl fumarate…" were included in cost-effectiveness analysis	These three treatments were only included for use as second-line therapy and this should be made clear in the Report (please note that natalizumab is also spelt incorrectly)
p230	States that Teva model "…in the base case, based on the subset of patients in the RSS who received this DMT."	This does not reflect Teva's submission. The RSS model used RSS data and the *de novo* model used results from Teva NMA as their base cases. It is sometimes unclear in the Report which of Teva's models is being talked about
p231	"The probability of cost-effectiveness for	Correct to Copaxone®

	glatiramer acetate (**Ccopaxone**) relative to best supportive care was…"	
Sections 14.2.3 - 14.2.22	The model referred to is not clearly specified	Can the AG clarify whether theses sections describe the *de novo* model submitted by Teva?
p233	Dose regimens in TEVA model stated as "300µg every other day" for IFN β-1b, "250µg every 2 weeks" for pegylated IFN β-1a and "500mg once daily" for fingolimod	These values were typographical errors within the model that did not affect the cost-effectiveness calculations. The correct values should be as *per* the SmPC for each product: 250*µ*g every other day for IFN β-1b, 125*µ*g every 2 weeks for pegylated IFN β-1a and 0.5mg once daily for fingolimod
P237	The Report questions the relapse cost and mortality rate used within the Teva model	Both of these points were addressed by Teva through scenario analyses, but this is not mentioned in Report
p238	Disutilities from adverse events are stated to be taken from "…manufacturer submissions to NICE for … IFN β-1a 44µg SC three times weekly (Rebif)."	This information was taken from the SmPC for Rebif
p239	Model assumptions stated to include "13. Patient access schemes for which data are publicly available are considered in the base case"	Teva model used current list prices in the base case
p248	States that Teva used "Natural history cohort based on London Ontario natural history cohort"	This is correctly stated on p231: British Columbia dataset was used for RRMS transitions. London Ontario data was only used for RRMS to SPMS and SPMS transitions
p248/9	Dose regimens in TEVA model stated as "300µg every other day" for IFN β-1b, "250µg every 2 weeks" for pegylated IFN β-1a and "500mg once daily" for fingolimod	These values were typographical errors within the model that did not affect the cost-effectiveness calculations. The correct values should be as *per* the SmPC for each product: 250*µ*g every other day for IFN β-1b, 125*µ*g every 2 weeks for pegylated IFN β-1a and 0.5mg once daily for fingolimod
p249	States that Teva used hazard ratio "…derived from 10 year RSS" and "Sensitivity analysis based on manuf NWMA…"	The RSS model used RSS data and the *de novo* model used results from Teva NMA as their base cases. Additional results from sensitivity analysis of NMA used for scenario analyses in *de novo* model
p251	States that "Relative risks of relapse were estimated from RSS data."	The RSS model used RSS data and the *de novo* model used results from Teva NMA as their base cases
p255	"Teva used the London Ontario data to derive the majority of their transition probabilities to model progression..."	This is correctly stated on p231: British Columbia dataset was used for RRMS transitions. London Ontario data was only used for RRMS to SPMS and SPMS transitions
p261	"Teva used the London Ontario dataset in order to model disease progression…"	This is correctly stated on p231: British Columbia dataset was used for RRMS transitions. London Ontario data was only used for RRMS to SPMS and SPMS transitions

p266	"We derived annual costs of £7264 and £6681 (£**6724**) for treatment with IFN β-1b 250µg every other day (Betaferon) and glatiramer acetate (Copaxone®) 40mg SC three times weekly or 20mg SC daily, respectively."	Value should be £6704 as stated in Table 68
p272 and p273	Hazard ratios from company submissions column states "Glatiramer acetate 20mg SC daily (Copaxone®)" and quotes redacted value from Teva's submission	This value was calculated for pooled Copaxone® data, as stated in Teva's submission
p276	Table 75, 'company estimates of effectiveness': from back calculation it appears that a hazard ratio of ~83% was used to drive the ICER for Copaxone®	The correct hazard ratio for Copaxone®, as supplied by Teva, was the "implied hazard ratio" using the year-10 RSS data: [redacted] (this value has been confirmed by the DoH)
p276	Table 75 states results for "Glatiramer acetate 40mg SC three times weekly (Copaxone®)"	This was pooled Copaxone® data, as stated in Teva's submission
Whole Report	Neutralising antibodies (NAbs) have been included within the scope of this appraisal but are only briefly mentioned in the Report and not considered during economic modelling	Teva's modelling indicates that NAbs have the potential to affect cost-effectiveness and so Teva requests the fact that they have not been included in the Assessment Group's model to be clearly stated in the Report

www.mstrust.org.uk

26 September 2016

Meindert Boysen
Programme Director, Centre for Health Technology Evaluation
NICE
10 Spring Gardens
London SW1A 2BU

Dear Meindert

Re: Assessment Report consultation: Multiple sclerosis - interferon beta, glatiramer acetate (review TA32)

Thank you for the invitation to submit initial comments on the technical content of the above assessment report. The MS Trust welcomes this MTA, marking the end of the Department of Health risk sharing scheme (RSS), a unique and innovative partnership that has delivered a huge amount for people with MS across the UK.

We would like to make the following points about the Assessment Report:

- Overall, we are encouraged by the conclusion that these agents are cost-effective in both RRMS and CIS.
- We are particularly encouraged by the conclusion concerning CIS, given the mounting evidence that early initiation of disease modifying drug therapy after a first demyelinating event can delay or stop conversion to clinically definite RRMS.
- Overall, we are pleased to see that NICE has based the cost effectiveness analysis for RRMS on the RSS analytical model. It is gratifying that the investment of time and energy by 5,000 people with MS and the neurologists and MS nurses working with them to collect this data over ten years has resulted in such a major contribution to our understanding of the benefits of these therapies over a longer time horizon.
- We are, however, concerned about some changes to the RSS model which are not justified by the data. We are aware that the DH is making a detailed response in this context and we support the DH response.
- We are also concerned that NICE is not using the actual price the NHS is paying in its cost effectiveness assessment. In the data circulated NHS list prices have been used which overstate the cost significantly.
- We have some concerns regarding Plegridy, principally because of the lack of long term usage data. We urge NICE to treat the estimates on Plegridy with caution and not use them in a comparative manner with the other DMTs.

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- We note that there is no inclusion of carer disutilities. It is our understanding that NICE included carer disutilites in other assessments, for example natilizumab. This inconsistency is not appropriate for a long term condition where severe disability is possible.
- The RSS data showed that discontinuation rates between the four drugs were very similar and a 5% discontinuation rate would be appropriate rather than calculating individual product assumptions from the original RCTs, which were over a short term.
- We welcome the research recommendations, particularly for further qualitative studies on the lived experiences of people with MS.
- We would welcome further research recommendations on a current definition of Best Standard Care, taking account of recent evidence and guidance about multidisciplinary MS care, and on the cost of relapse, taking account of social care and the wider personal and societal costs alongside healthcare costs.
- The wealth of real-world experience of these agents has certainly confirmed that at an individual patient level, different products will suit different individuals. Dosing schedules, storage, side-effects and tolerability will vary, so we stress that. having been shown to be clinically and cost-effective, **all these products should remain available as a treatment option for all eligible patients**.

We look forward to the upcoming Appraisal Committee Meeting on 2nd November.

Yours sincerely

Amy Bowen
Director of Service Development
MS Trust

Assessment Report consultation: Multiple sclerosis - interferon beta, glatiramer acetate (review TA32) [809]

Response on behalf of Association of British Neurologists

26th September 2016

Note:

- MD also nominated by ABN to act as clinical expert in respect to this assessment
- Has been clinical lead for UK Risk Sharing Scheme
- Please see full declarations in accompanying documents

Introductory comments

1. This represents an ambitious and extensive piece of work by the assessment group. The methods and conclusions are transparent, well presented and comprehensible. The strategies for identifying relevant studies are well-defined. The agreed protocols appear to have been followed as intended. The review is clear, without apparent bias and credible.

2. With the exception of Plegridy, these drugs have been used extensively in the NHS, especially since the set up of the RSS in 2002. As neurologists, we approach this review with broad and long personal experience of using the medications, offering a different perspective than might be more usual in a NICE assessment of an emerging technology.

   The advent of newer therapies has led to marked changes in the way these drugs are used. In many centres, it is now unusual for naïve patients to choose an injectable therapy first line. Even before the advent of escalation therapies (natalizumab and fingolimod initially), switching between these drugs for reasons of tolerance and efficacy was common. The advent of newer therapies has meant that the models proposed here, whereby a patient is expected to stay on any one therapy long term, lack face validity.

   The history to this is, however, well known, and the 2002 decision that the drugs were not cost effective in the then-favoured model, has needed to be revisited for some time. The end of the RSS offers this opportunity, however, this exercise must be seen as very artificial and divorced from current practice, albeit an essential prerequisite to the subsequent evaluation of the newer therapies and evolving treatment strategies.

3. It is important to treating physicians that the assessment's findings, albeit they are largely in favour of the drugs, are credible and robust to criticism, and potential areas of weakness are highlighted.

4. The prescribing community would value as wide a range of choices at each stage of the disease as is possible, allowing prescribing of drugs within the available clinical evidence and permitting patients a choice of initial therapy based on their needs and values, along with the chance to switch as dictated by tolerance or efficacy. Any proposed restriction placed on physician or patient choice by cost considerations, coming at this late stage in established practice, would require careful justification.

5. The assessment highlights the sometimes large and unpredictable effects of challenging underlying assumptions in the models. One of the main concerns with this appraisal is the potential impact of the outcome on the assessment of newer therapies. A good "sense check" on the final model would have been to see how some of the newer drugs, which are clearly superior to this group in terms of efficacy in day to day practice, would perform. It is an oddity of the way things have been done that we need to wait to look at a drug such as natalizumab which would have acted as a useful internal control of the power of these methods to detect a true difference. There is a risk that this assessment might need critically revisited if blatant inconsistencies emerge from later assessments based on these methods.

6. Any advice offered on future studies must be realistic for this appraisal's conclusions to maintain credibility. It is unlikely we will see any of these drugs used even in the control arm of a future DMT trial, so to propose a head to head or placebo controlled trial is pointless. At best, one might express regret that the chance to do such as study has been missed.

Major points:

1. The reasons for the focus on ARR, TTP3 and TTP6 as outcome measures in the NMA are clear, but the authors do little to justify how these equate to long term outcomes, or the justification for assuming any effect, let alone a sustained effect beyond the 2-3 years of the trial data. As key to the process, this should be discussed.
2. the term TTP is ambiguous:
    a. An important recent publication (Lublin et al Neurology 2014; 83:278) creates an important difference between *worsening* of the EDSS (which can be relapse driven, reversible, or driven by neurodegenerative mechanisms) and *progression* which should be reserved for irreversible deterioration of the EDSS on a presumed neurodegenerative basis. The use of the term progression in reference to short term outcomes unduly suggests a neuroprotective role for the drugs, or implied effect in delaying the

onset of SPMS. It would be best if this distinction were made throughout the document in line with modern usage.

b. This is particularly important when knowingly choosing TTP3 over TTP6 in the full knowledge that many of these worsenings are reversible and will not contribute to long term disability
c. The wording itself is misleading. MS trials often have, for example, "time to EDSS 6" as an outcome measure. An effective therapy will delay time to EDSS 6, and this will be expressed as a time. This seems quite distinct to the use here:
"For example, a hazard ratio of 0.75 in group 1 as compared to group 2 means that at a point in the future, people without progression group 1 will have a 25% less chance of having disability progression as compared to people without progression in group 2."
This refers to the risk of having progressed at a fixed (though variable between studies) time point. The HR does not reflect the *delay* to any disability milestone or fixed progression, and I find the term confusing in this regard
d. Assuming the method is understood correctly, this may unduly favour drugs with a short study (eg Plegridy) vs those with a long study (eg Betferon), if there is a genuine waning effect, as seen in the RSS, where there was a particularly marked year 1 effect, partially cancelled out by subsequent years. If only using "the point of data maturity" this may lead to erroneous conclusions.
e. On a similar note, "Time to clinically definite MS" is used in the CIS analysis. Similar to the point on TTP3, this is misleading at first read. Again, you appear to mean "chance of having CDMS at a specific time point", not delay as expressed by time to eg median survival against the measure.

3. It is unclear what triggers inclusion of particular findings in the abstract
    a. The ARR result for GA in the NMA is included but the TTP3 results for R44 is not. Given that neither metric is shown as superior for ranking drugs in terms of long term efficacy, it may be a worry that, especially on casual reading, superiority of GA in other domains might wrongly be assumed
    b. Plegridy is also given prominence in the summary, despite results being derived from a short trial. These results should be treated with more caution

4. The CIS analysis is immediately out of date following the McDonald 2010 revisions (McD10). The term CIS has essentially been redefined between the time the studies were initiated and this analysis. It is not clear enough that this is a study of first demyelinating events representing a mix of early MS and true CIS. There must be no room for these conclusions to be applied uncritically to a "pure" CIS group. It is a shame that patient level data could not have been accessed to allow for a true appraisal of the CIS data and also, from the early MS subgroup, to inform models on early treatment of MS proper.

5. Especially given the uncertainty here, giving a clear steer on the superiority of one product in terms of cost effectiveness for CIS seems unsafe.
6. There is no recognition of different epochs of studies. This is a major, and well known, area of controversy in RRMS. There is nearly 20 years between the start of the Betaferon study and the Plegridy study. The patients forming the placebo arms are very different, and this has been extensively commented upon. At the simplest level, the ARR in the placebo groups differ greatly with trial epoch. Especially in the NMA, it appears the PBO groups are seen a constant, but it is not clear to what extent there is baseline matching or adjustment, and even with good methods, we know that people going into a PBO controlled trial in 2010 are a very self-selected group compared to 1988. This makes any attempt at network analysis at best risky, and there is little reassurance in the text that the technique is valid in this setting. While the results are, overall, not controversial, the apparent prominence given to Plegridy would seem to demand more qualification.
7. Section 13.1.12 – was the RSS subgroup used? It should be noted that the RSS used a subgroup of BCMS, selecting 898 patients eligible for DMTs under strict 2002 ABN guidelines. The average age was 37 and disease duration 8 years. This is quite different to current practice, and, importantly, it is not clear how valid it is to use these transition probabilities for a model starting at age 30, with, presumably, a mean disease duration of 3 years. Were fresh TPs derived for this cohort, perhaps bypassing the need for 2 relapses in the previous 2 years? It is not clear if this is the case.
8. For RRMS, we need more clarification on whether the RSS baseline (based on real patients on treatment compared to a synthetic cohort) or a completely synthetic model extrapolated from 2 year studies (as in SA1), is more valid. We would not want to complain about the more favourable outcome in SA1 and the choice it gives patients and physicians - and there exists a potential challenge from the PSA on the RSS model - but the RSS was established to address the very question of long term assumptions in cost effectiveness models. SA1 suggests tolerance for substantial price increases against a willingness to pay of even £20k which may not be justified.
9. The trial data reviewed here includes studies that are old, familiar and have been repeatedly re-analysed and presented. In line with their principles, the assessors have not included the wealth of real world data available on the comparative efficacy of these drugs and the changing ways in which they are employed. While the UK community is familiar with NICE's methods, the exclusion of potentially informative data, such as that available from MS BASE, on discontinuation rates, switching rates and comparative efficacy, should be explained, especially when it is replaced with assumptions and extrapolations from 2 year studies.

Minor points – in order through the document

1. Section 4.1 TA32: insufficient evidence on *long-term* effectiveness; again 5.4. Short term effectiveness was accepted
2. peak incidence 40-45– this needs clarified. The MacKenzie paper based on GP records is an outlier from all others at 25-30 – in line with figures used later in this paper
3. section 5.1 – "2 or more genes" (>100 variants; rev Sawcer, Lancet 2014) – later section clarifies this, but reads oddly at this point
4. section 5.2: RES/ HA used incorrectly in 5.2. Terms defined by FDA/EMA only, not international consensus on their definition or significance
5. section 5.2: in line with *Lublin et al Neurology 2014; 83:278* you should avoid the term "benign MS'
6. section 5.2: CIS will not develop into PPMS
7. R22 as well as R44 licensed for SPMS
8. section 5.4.2 – it is perhaps inviting unwanted comment to venture into these areas. EBV by Vienna consensus not isolated from B cells in MS despite early reports *(Owens et al. MSJ 2012)*
9. section 5.4.3 – imaging section not great – Gd not a "contrast" agent; oddly worded re chronic plaques and enhancement; no mention of MR measures of neurodegeneration which correlate better with longer term disability
10. CDMS – meaningful only in CIS trials, and now of uncertain significance – in most cases, no more than time to second relapse in a patient with MS. Probably best introduced as an obsolete term
11. section 5.6.1 – reword to make clear FSS are combined to form the DSS, or EDSS (later evolution of the original)
    a. avoid term *wheelchair confinement* – focus on retained ability
    b. avoid term *benign MS*
    c. risk factors – clarify phenotype
12. section 5.6.2 – effect of relapses on long term progression – effect of early vs late relapses probably worth a mention. Given this, should GA be given prominence on ARR data, and should abstract include a qualification on extrapolation of short term measures to long term efficacy
13. section 6.1: NAbs in practice – should reflect heterogeneity of practice – not universally tested in clinical practice but some centres do. Statement may reflect advisors practice, but testing is routine in many sites.
14. SmPC on Rebif – "relapsing MS" is used - not the same as RRMS
15. HA – for nat – again care in use of terms HA/ RES
16. Section 6.3 incorrect escalation criteria – see SMpC for fingo – does not require multiple relapses
17. Exclusion of proportion relapse free as an outcome measure is too dismissive. FDA have preferred this to prevent high relapsing individuals skewing figures. I think this demands more recognition as desirable, even though it is not available for many of the studies you review.
18. Steroid Rx and grading of severity is dependent on countries involved – some have mandatory hospitalization for steroids. It is hard to compare these between studies unless definitions have been standardised
19. CIS: discontinuation for all seems very low (face value vs PreCISE discontinuation of c13% in 2 years (*Comi et al. Lancet 2009*))

20. GA best but the cost effectiveness (albeit at a higher ICER) of Betaferon could be clearer

REVIEW OF TA 32: BETA INTERFERON AND GLATIRAMER ACETATE FOR TREATING MULTIPLE SCLEROSIS

Comments from the Department of Health on the Assessment Group's report

We welcome the decision by the Assessment Group (AG) to use the model developed for the UK Multiple Sclerosis (MS) Risk Sharing Scheme (RSS), and many of its parameter estimates, for their base run. We agree with the AG's view that the long-term follow-up of patients in the RSS makes it a more robust basis for estimates of cost-effectiveness over the lifetime duration of MS than the short-term estimates derived from the pivotal RCTs.

2. However, we are concerned at some of the changes in assumption proposed by the AG, in particular in relation to the calculations for individual disease modifying therapies (DMTs). In some cases, naturally, the changes reflect the AG's professional judgement which we respect, even if we may not always agree with it. However on some important aspects we believe that the AG's changes are based on a misunderstanding of the material supplied by the Department, on behalf of the RSS Funders' Group, and by the individual companies. We consider that this could result in a misleading impression in particular of the relative cost-effectiveness of the individual DMTs. In addition, we think that the way in which the AG have carried out the probabilistic sensitivity analysis could exaggerate the dispersion about the central values and thus underestimate the probability of achieving any likely cost-effectiveness threshold.

3. Our main concerns are as follows:

i *Relative rates of disease progression.* For the calculations on individual DMTs (AG calculations SA2a and SA2b, and the calculation for Plegridy in SA3) the AG has used relative hazard rates for disease progression derived from RCT data as a direct input to the RSS model. Unfortunately, this is not valid. The reasons are set out in detail in an Annex to the report on the year 6 analysis by the RSS Scientific Advisory Group[1] which formed part of the documentation supplied to NICE (see attached extract at Appendix 1). In brief the use of hazard rates for (net) forward disease progression will give an exaggerated impression of the effect of DMTs in slowing disease progression when used in a model which assumes that "backward" transitions (disease regression) are unaffected by treatment.

In our view, the most robust way of estimating the effects of individual DMTs on disease progression would be to use the "implied hazard ratios" derived from 10-year RSS data for individual products (comparable to the hazard ratio of 0.7913 for the DMTs in aggregate which the AG have adopted for their base run). These implied hazard ratios will have been supplied by the individual companies as part of their submissions to NICE and appear to be the basis for the parameters used for Avonex and Rebif 44 in AG calculations SA3. (There appears to be a problem with

Copaxone where the results reported in table 75 are much less favourable to the product than we would have expected.)

We appreciate that there is an issue with Plegridy, where 10-year follow-up data from the RSS are not available. From the evidence presented by the AG Plegridy appears to have a greater treatment effect in the short term than other interferon beta 1a preparations such as Avonex, but it would be hazardous to assume that this will remain true over longer periods. There is no obvious solution to this dilemma, but we do suggest that the estimates presented by the AG for Plegridy should be treated with considerable caution, and in particular that the cost-effectiveness of the other DMTs should be assessed against best supportive care rather than against Plegridy (as the apparently cheapest treatment option).

ii *Carer disutilities.* The AG have not included carer disutilities in their base run, although they do include them in a sensitivity analysis in an appendix. Our understanding is that there is precedent for including carer disutilities in the base run in other NICE appraisals, eg the appraisal of Natulizumab[2]. We consider that, for a long-term condition in which patients are likely to need considerable help from informal carers for substantial periods of their life, it would be reasonable to include the quality of life impact on carers as part of the assessment.

iii *Discontinuation rates.* The AG rightly draw attention to the potential impact of discontinuation rates on estimates of cost-effectiveness. (Perhaps paradoxically, a higher discontinuation rate in the RSS model results in better cost effectiveness – lower cost per QALY – though this may well be an artefact of the model assumptions.) However, their report does not make clear that the assumption of a 5% discontinuation rate included in the RSS model (and in the AG's base case) is derived from RSS data, reflecting long-term follow-up of patients under "normal" clinical conditions, rather than an arbitrary assumption. Our analysis also showed that there are only very small differences in the discontinuation rates between the 4 DMTs in the RSS. We consider that, in comparing the cost effectiveness of individual DMTs, it would be more robust to use a common assumption of a 5% discontinuation rate rather than the very different estimates derived from the individual RCTs.

Iv *DMT acquisition costs.* For two of the 4 DMTs in the RSS, NHS patients will for the foreseeable future be able to access the drugs at a lower effective price than the NHS list price, through arrangements comparable to a patient access scheme. Details of these arrangements will have been supplied to NICE in the relevant company submissions. In one case, the discount below NHS list price is very significant. We will be responding separately to a query from the NICE's Programme Director about the status of these "effective NHS prices", but there is a case for saying that they should be used, rather than the NHS list prices, in order to give a fair comparison of the cost effectiveness of the 4 products.

v *Rebif.* For Rebif, two doses (22 mcg and 44 mcg) are licensed for use in the UK. The AG group have only considered the cost-effectiveness of Rebif 44, but the evidence from the RSS shows that a substantial proportion of patients (about one-third) remain on or are titrated down to the lower dose. We consider that this should be taken into account to give a fair comparison between Rebif, as used in normal UK clinical practice, and the other DMTs.

vi *Handling uncertainty over long-term treatment effects ("waning").* The AG's base case uses a 50-year horizon (in effect, a lifetime horizon) in line with NICE guidance that the time horizon should reflect the long-term effects of treatment. We agree that this is entirely appropriate. However, even using RSS data we only have evidence on the treatment effects of the DMTs for 10 years. To reflect uncertainty over the treatment effect for the much longer periods involved in modelling, the parties to the RSS agreed that it would be reasonable to apply a 50% reduction to the effect of treatments on disease progression after year 10 of the projection. This is in line with precedents from other NICE appraisals where long-term effects have to be extrapolated from shorter-term data, eg the appraisal of natulizumab[3].

This "waning assumption" is referred to in the AG's chapter 14 (the critique of the company submissions) but is not discussed at all in chapter 15 (the AG's base case and sensitivity calculations). We consider that the Appraisal Committee should have access to calculations of cost effectiveness both with and without "waning", both for the DMTs in aggregate and for individual DMTs.

vii *Baseline EDSS distributions.* The cost-effectiveness of treatment is sensitive to the assumption made about the distribution of patients over EDSS states at the start of treatment (the "baseline EDSS distribution"). Broadly, the higher the proportion of patients in higher EDSS states, the less the opportunity to benefit from treatment and the less favourable the cost-effectiveness ratio. In the RSS, we noted some differences in the baseline EDSS distributions for the different DMTs and we used product-specific distributions in the price adjustment calculations specified by the scheme. However, we agree with the AG's implicit assumption in the calculations presented in chapter 15 that the same distribution should be used for each DMT in order to allow a like for like comparison.

viii *Probabilistic sensitivity analysis.* We were surprised at the AG's finding that a number of replications showed treatment to be dominated by best supportive care (higher cost and lower QALYs). On investigation, we believe this is due to a combination of two factors: (a) use of the very wide confidence intervals on the utility associated with different EDSS states taken from the 2001 ScHARR model, (b) the assumption that each of these utility values can vary independently around its central value. Taken together, these assumptions lead to the implausible result that in

some replications a patient can move to a better quality of life (higher utility) as a result of moving up one or more EDSS levels. In addition, use of these (in our view) extreme assumptions results in exaggerating the dispersal of the resulting cost per QALY about its central value and thus, other things being equal, an underestimate of the probability of achieving any likely cost per QALY threshold.

4. With the modifications discussed above, but otherwise accepting the AG's preferred assumptions (mortality, relative rate of relapse, same baseline EDSS distribution for each product) our calculations of the ICER for the DMTs in aggregate and for the 4 products in the RSS, with and without waning, are as below:

DH estimates of cost-effectiveness ratios using the RSS model and year 10 data[a]

DMT	Without "waning"			With "waning"		
	Net cost (£)	Net QALYs	ICER (£ per QALY)	Net cost (£)	Net QALYs	ICER (£ per QALY)
All RSS DMTs[b]	25,473	1.047	24,329	29,572	0.900	32,847
Avonex	[redacted]					
Betaferon	[redacted]					
Rebif[c]	[redacted]					
Copaxone	[redacted]					

a. Final net RSS prices; "implied hazard ratios" and discontinuation rates from the year 10 RSS data; relative relapse rates from the AG; including carer disutilities; SMR for general mortality = 1 as in the AG's base case
b. Weighted average of all DMTs in the RSS, using the relative proportions in the RSS cohort as the weights
c. Weighted average of estimates for Rebif 22 and Rebif 44, using the relative proportions in the RSS cohort as the weights

5. Using these modifications and the additional assumptions set out in Appendix 2, our estimates of the probability of achieving various cost-effectiveness thresholds for the DMTs in aggregate are as follows:

Threshold (cost per QALY)	Probability of an ICER equal to or lower than threshold:	
	Without waning	With waning
£20,000	29.0%	4.9%
£25,000	53.1%	17.5%
£30,000	72.2%	38.5%
£36,000*	86.4%	62.0%
£40,000	91.8%	74.4%
£45,000	95.6%	84.7%
£50,000	97.6%	91.3%

*Threshold agreed for the purpose of the 2002 Risk Sharing Scheme

6. Some detailed comments on the AG's report are at Appendix 3.

Department of Health
Medicines, Pharmacy and Industry Division
September 2016

References

[1] Scientific Advisory Group to the UK MS Risk Sharing Scheme *Report on the year 6 analysis* (DH July 2014)
[2] NICE TA 127 *Natulizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis* (NICE August 2007)
[3] See reference 2

APPENDIX 1: EXTRACT FROM THE REPORT OF THE SCIENTIFIC ADVISORY GROUP ON THE YEAR 6 ANALYSIS

Annex D: adjustment of the hazard ratios for the Markov model

D.1 The original ScHARR model, a conventional discrete Markov model, did not "allow" transitions to lower EDSS values (transitions representing disease improvement). To model the effect of treatment with a DMT, it was assumed that all transition probabilities representing a forward transition (disease progression) were multiplied by a common factor, the hazard ratio. This was in turn derived from the relative time to sustained disease progression as estimated from the original RCTs.

D.2 The new Markov model, derived from the BCMS dataset for use in the year 4/ year 6 analysis, allows backward transitions and the estimated transition probabilities are substantial. The issue therefore arises of how the impact of DMTs on these transition probabilities should be modelled. We considered three options:

i Method 1 – backward transition probabilities are multiplied by the same factor as forward transitions (ie treatment with a DMT reduces the probability of a backward transition);

ii Method 2 – backward transition probabilities are unaffected by treatment with a DMT;

iii Method 3 – backward transition probabilities are multiplied by the inverse of the factor used for forward transitions (ie treatment with a DMT increases the probability of a backward transition).

Method 1 is plausible only if it is assumed that apparent backward transitions represent the effect of measurement error, or recovery from an unidentified relapse, rather than a true improvement in the patient's condition. Method 2 corresponds to the hypothesis that DMTs can slow the processes which lead to disease progression but cannot reverse any physical change which has already occurred. Method 3 corresponds to the hypothesis that DMT treatment can actually result in an improvement in the patient's underlying health status. Our final advice was that we should take a "neutral" assumption for the purpose of the year 4/year 6 analysis, ie method 2 above, and this is incorporated in the Statistical Analysis Plan for the year 4/ year 6 analysis. We may wish to return to this issue for year 8.

D.3 The choice of method has important consequences for the way in which the hazard ratio should be interpreted. Compare the two highly simplified models in figure D1, where the model in the upper part of the diagram represents a model without backward transitions and that in the lower part of the diagram one with both backward and forward transitions. With the transition probabilities shown, the expected net change in EDSS in one year is 0.1 in each case. However, if the forward transition probabilities are reduced by 25% the expected net change in EDSS for the first model is also reduced by 25%, while in the second model it is reduced by 50% (from a net change of 0.2 – 0.1 = 0.1 to a net change of 0.2*0.75 – 0.1 = 0.05).

D.4 We have modelled this effect more systematically with a simplified version of the Markov[1] model used for the main year 6 analysis. The results are shown in figure D2, which plots the relative rate of disease progression (ratio of change in average EDSS from baseline to year 10, comparing "treated" with "untreated" patients) as a function of the hazard ratio. As expected, for method 1 the relative rate of disease progression is very similar to the hazard ratio (as it would be for a model like the ScHARR model without backward transitions). For method 2 the relative rate of disease progression is progressively lower than the hazard ratio, and for method 3 the difference is even more extreme.

D.5 We need to take account of this effect in order to make a fair comparison between the "target" hazard ratios established in 2002 (intended for use with the ScHARR model) and the "implied hazard ratios" resulting from the year 6 analysis. Our proposed method is to use the line corresponding to method 2 in figure D2 in reverse, ie to find the value of the hazard ratio which would give a relative rate of disease progression (over 10 years and expressed as the change from baseline in average EDSS) of exactly 0.6, 0.7 or 0.8. The resulting "adjusted hazard ratios" are given in the table below:

Original hazard ratio	Adjusted hazard ratio
80%	88.0%
70%	82.4%
60%	76.9%

[1] The only difference is that we have ignored MS and non-MS deaths. For the relatively short time periods considered this is unlikely to have any significant effect.

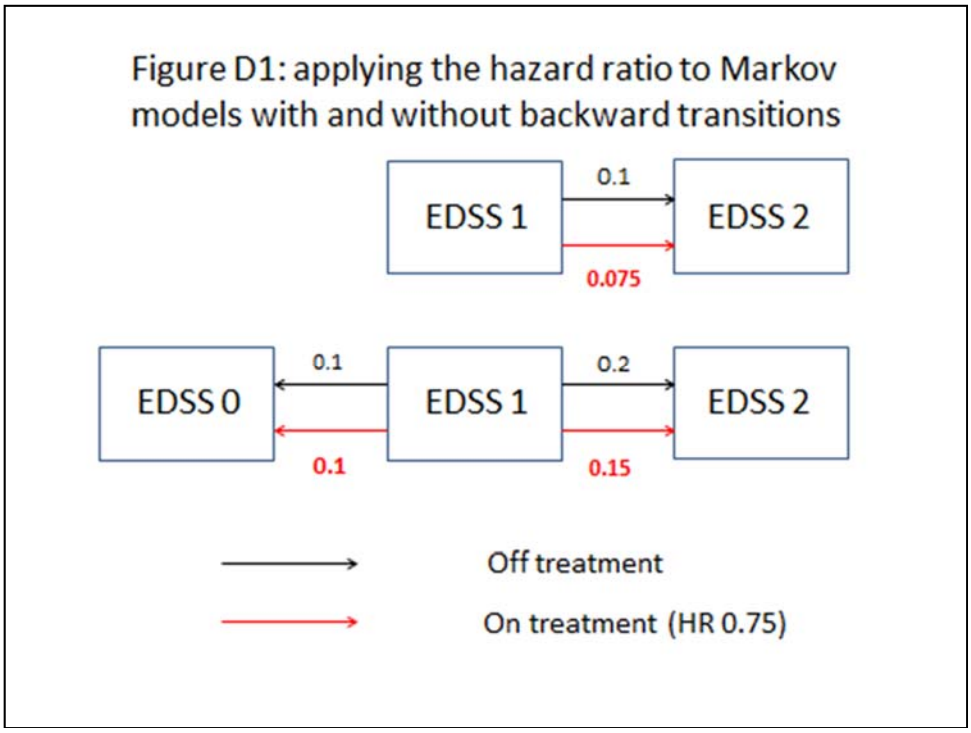


Figure D1: applying the hazard ratio to Markov models with and without backward transitions
EDSS 1
EDSS 2
0.1
0.075
EDSS 0
EDSS 1
EDSS 2
0.1
0.2
0.1
0.15
Off treatment
On treatment (HR 0.75)

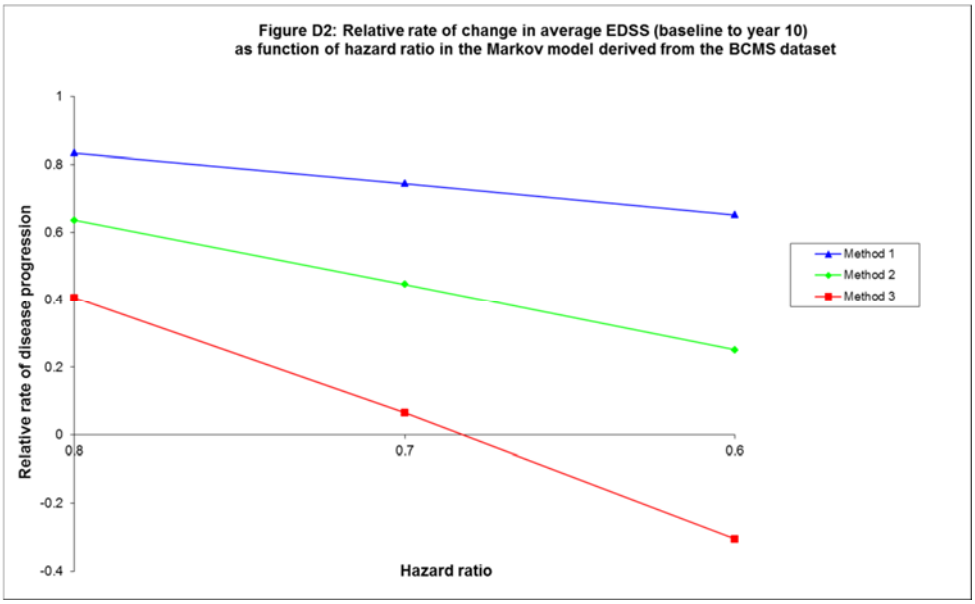


Figure D2: Relative rate of change in average EDSS (baseline to year 10) as function of hazard ratio in the Markov model derived from the BCMS dataset
Relative rate of disease progression
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
0.8
0.7
0.6
Hazard ratio
Method 1
Method 2
Method 3

APPENDIX 2: PROBABILISTIC SENSITIVITY ANALYSIS

This appendix gives further details of the probabilitistic sensitivity analysis described briefly in the covering note.

Assumptions

2. Central values for input parameters are those used for the deterministic analysis described in para 4 of the covering note. The basic assumptions for the distribution of the variable parameters are as follows:

Parameter	Distribution	Central value	Confidence intervals	Source/comments
Hazard ratio for forward progression	Log normal	0.7913	0.7708, 0.8123	Analysis of RSS year 10 data ("implied hazard ratio"
Relative rate of relapse	Log normal	0.7310	0.6118, 0.8309	Central value is weighted mean of AG estimates; parameter for variation about central value from AG
State costs:				
EDSS 0	Log normal	1,195	+/- 10%	Central value from ScHARR model, variation as in AG report (arbitrary assumption)
EDSS 1		1,195		
EDSS 2		1,195		
EDSS 3		2,203		
EDSS 4		2,283		
EDSS 5		8,045		
EDSS 6		8,974		
EDSS 7		27,385		
EDSS 8		42,521		
EDSS 9		54,055		
Cost of a relapse	Log normal	4,263	+/- 10%	Central value from ScHARR model, variation as in AG report (arbitrary assumption)
Utilities:				
EDSS 0	Log normal	0.9248	0.8650, 0.9581	Central values from IMS meta-analysis of MS Trust and Heron datasets. Confidence intervals from DH analysis of the same data. The log normal distribution is applied to the difference between the utility for the given state and the utility for perfect health (1).
EDSS 1		0.7614	0.7079, 0.8051	
EDSS 2		0.6741	0.6165, 0.7230	
EDSS 3		0.5643	0.5143, 0.6092	
EDSS 4		0.5643	0.4965, 0.6230	
EDSS 5		0.4906	0.4333, 0.5421	
EDSS 6		0.4453	0.3722, 0.5099	
EDSS 7		0.2686	0.2190, 0.3150	
EDSS 8		0.0076	-0.0705, 0.0800	
EDSS 9		-0.2304	-0.3086, -0.1569	
Disutility of a relapse	Log normal	-0.0277	+/- 10%	As for cost of relapse

3. Three variants were considered:

In variant (1), the parameters representing the costs for the various EDSS states were assumed to vary with perfect correlation about their central values (a single random number in the interval [0,1] was used to calculate the sampled value of each parameter). The underlying assumption is that the central values correctly describe the *shape* of the curve of cost versus EDSS, and that the only uncertainty relates to the *scale* of the curve. Similarly the utility values for the various EDSS states were assumed to be perfectly correlated;

In variant (2), the parameters for the utilities of the EDSS states were sampled independently from their respective distributions;

In variant (3), the parameter determining the distribution of the relative hazard ratio for forward progression was multiplied by a factor of 3. As we noted in submitting evidence from the RSS year 10 analysis to NICE, the confidence intervals we supplied reflect only sampling error in the RSS dataset (*n = 4,862*) and not the uncertainty in the transition probabilities in the Markov model drawn from the BCMS dataset (*n = 898*). Sampling error in parameters derived from the BCMS dataset will be of the order of $\sqrt{(4,862/898)}$= ~2.3 as great as sampling error in the RSS dataset. Sampling error from the two sources together will be of the order of $\sqrt{(1^2 + 2.3^2)}$ =~ 2.5 as great as sampling error from the RSS dataset alone. Multiplying the distributional parameter by a factor of 3 therefore represents a conservative estimate of the true uncertainty associated with the relative hazard ratio for forward progression.

All calculations were carried out both with and without the "waning" assumption used for the deterministic calculations (a 50% reduction in the treatment effect from year 11 onwards).

Results

4. The key results from variant (1) are shown in the table below, and in figures 1a/1b (without waning) and 2a/2b (with waning):

Probability of achieving a given cost per QALY threshold: variant (1)

Threshold (cost per QALY)	Probability of an ICER equal to or lower than threshold:	
	Without waning	With waning
£20,000	10.7%	0.0%
£25,000	56.0%	1.7%
£30,000	92.6%	23.7%
£35.000	99.5%	69.4%
£36,000*	99.7%	77.2%
£40,000	100.0%	94.7%
£45,000	100.0%	99.5%
£50,000	100.0%	100.0%

*Threshold agreed for the purpose of the 2002 Risk Sharing Scheme

The ICER values form a relatively tight distribution around the central values of respectively £24,300 (without waning) and £32,900 (with waning); in 10,000 replications, no instance occurred in which the treatment strategy was "dominated" by best supportive care (lower QALYs and higher cost).

5. The results for variant 2 were very similar to those for variant 1. With 10,000 replications, the distribution of the ICER about its central value for variant 2 (95% confidence intervals with waning £25,352, £41,851) is only marginally wider than for variant 1 (£25,577, £41,580).

6. Variant 3, as expected, does result in a rather looser distribution about the central values – see the table below, and figures 3A/3B (without waning) and 4A/4B (with waning):

Threshold (cost per QALY)	Probability of an ICER equal to or lower than threshold:	
	Without waning	With waning
£20,000	29.0%	4.9%
£25,000	53.1%	17.5%
£30,000	72.2%	38.5%
£35.000	84.5%	58.6%
£36,000*	86.4%	62.0%
£40,000	91.8%	74.4%
£45,000	95.6%	84.7%
£50,000	97.6%	91.3%
£55,000	98.8%	94.9%
£60,000	99.2%	97.1%

*Threshold agreed for the purpose of the 2002 Risk Sharing Scheme

The mean cost per QALY is also shifted, from £24,300 for the deterministic calculation to £25,900 for the stochastic calculation (without waning) and from £32,800 to £34,600 (with waning). This is because the distribution of cost per QALY values is significantly skewed to higher values. However, even in 10,000 replications we did not observe any example in which the treatment strategy was dominated by best supportive care – the lowest incremental QALY for the version with waning was 0.365 and the highest cost per QALY was £120,300.

<u>Discussion</u>

5. The very small difference between variants 1 and 2 is perhaps surprising – one might have expected to see a significantly larger spread of values about the mean for variant 2, in which the EDSS-specific utilities are allowed to vary independently, as compared to variant 1 in which they are correlated. Presumably this reflects the relatively low sensitivity of the overall cost per QALY to the detailed shape (as opposed to overall scale) of the utility versus EDSS curve, as well as the relatively narrow confidence limits on the utility estimates derived from our re-analysis of the MS Trust and Heron data.

6. In contrast, use of the wider confidence intervals on the relative hazard ratio for forward progression (variant 3) results in a significantly wider spread of ICER values. This is consistent with the finding, from the AG's univariate sensitivity analysis as well as from our own observations, that the cost per QALY is particularly sensitive to this parameter. This is hardly surprising – it is the effect of the DMTs in reducing the rate of progression to the higher EDSS levels, where utility is greatly reduced and the cost of supportive care increases sharply, which is largely responsible for the overall QALY gain and for moderating the net cost of treatment.

7. Even with these deliberately extreme confidence intervals we did not confirm the AG's finding that a proportion of replications occur in the "North West quadrant" in which the treatment strategy is dominated by best supportive care (lower QALYs and higher costs). We consider that this finding is most likely the result of the use of extremely wide (and in our view implausible) confidence intervals on the EDSS-specific utilities.

8. We consider variant 3 (with "waning") to be the best available representation of the uncertainty in the cost effectiveness estimates presented in the covering note. In these calculations, we have allowed variation in those parameters which, from the AG's univariate sensitivity analysis, have the greatest impact on the overall cost per QALY. The distributions of these parameters reflect as far as possible the empirical evidence, or are reasonable guestimates. For the hazard ratio for forward progression, we have adopted a deliberately conservative assumption which allows both for sampling error in the BCMS dataset from which the Markov model is derived, and for the sources of potential bias in our estimate of the "implied hazard ratio" [see reference 1 to the covering note]. Finally, as argued in the covering note, the use of a "waning" assumption (a 50% reduction in the treatment effect from year 11 onwards) allows for the inevitable uncertainty in projecting forward the treatment effect over the lifetime horizon needed to capture the full benefits and costs of treatment. Adopting a more modest reduction, or repeating the calculations without any waning, shifts the acceptance curve towards lower costs per QALY without significantly changing its shape.

Figure 1: Scatterplot and acceptance curve for variant 1, without waning (10,000 samples)

Figure 1a

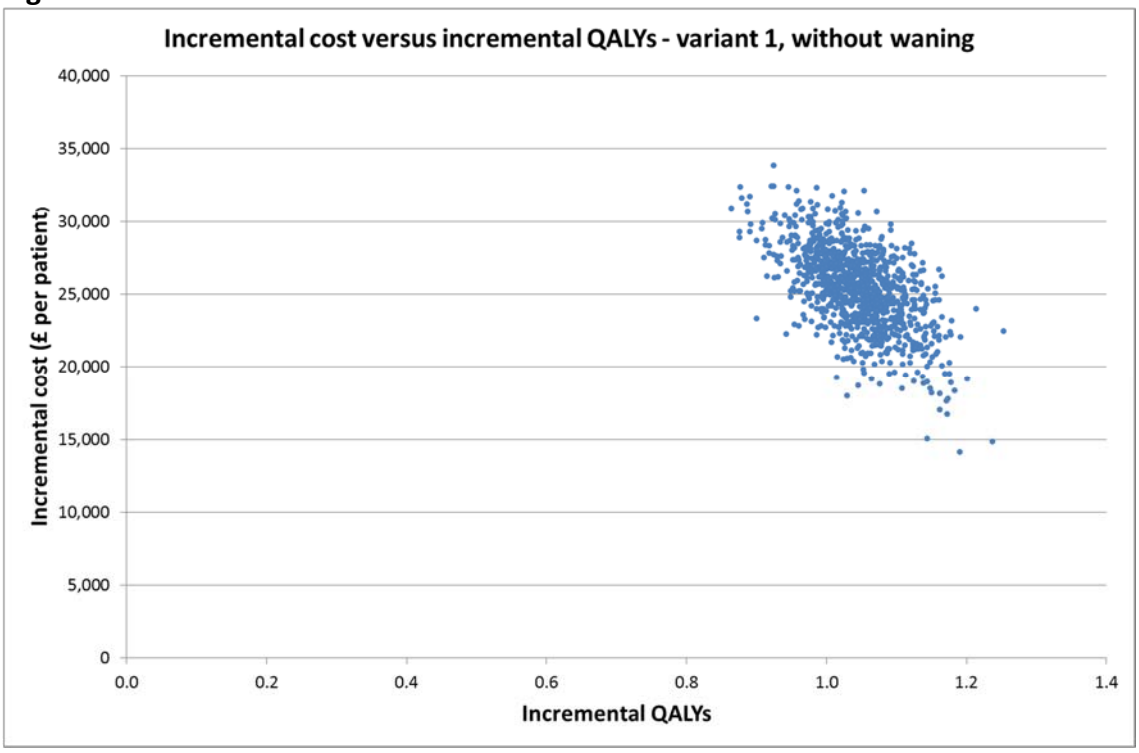


Figure 1b

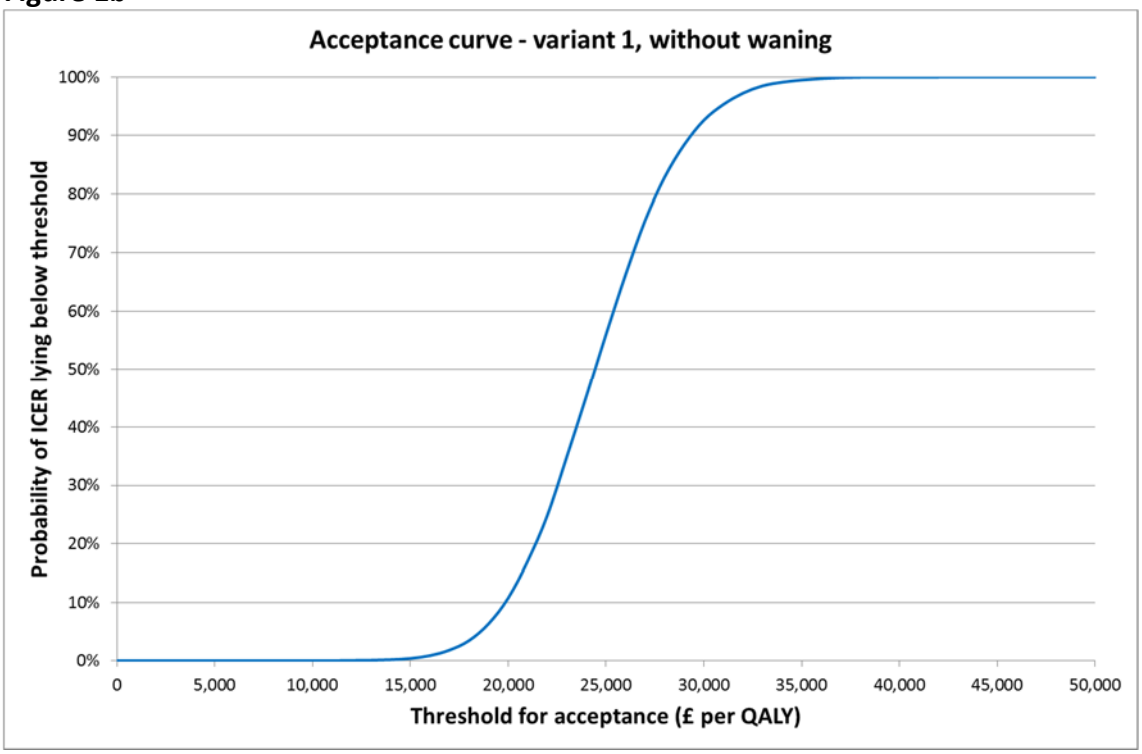


Figure 2: Scatterplot and acceptance curve for variant 1, with waning (10,000 samples)

Figure 2a

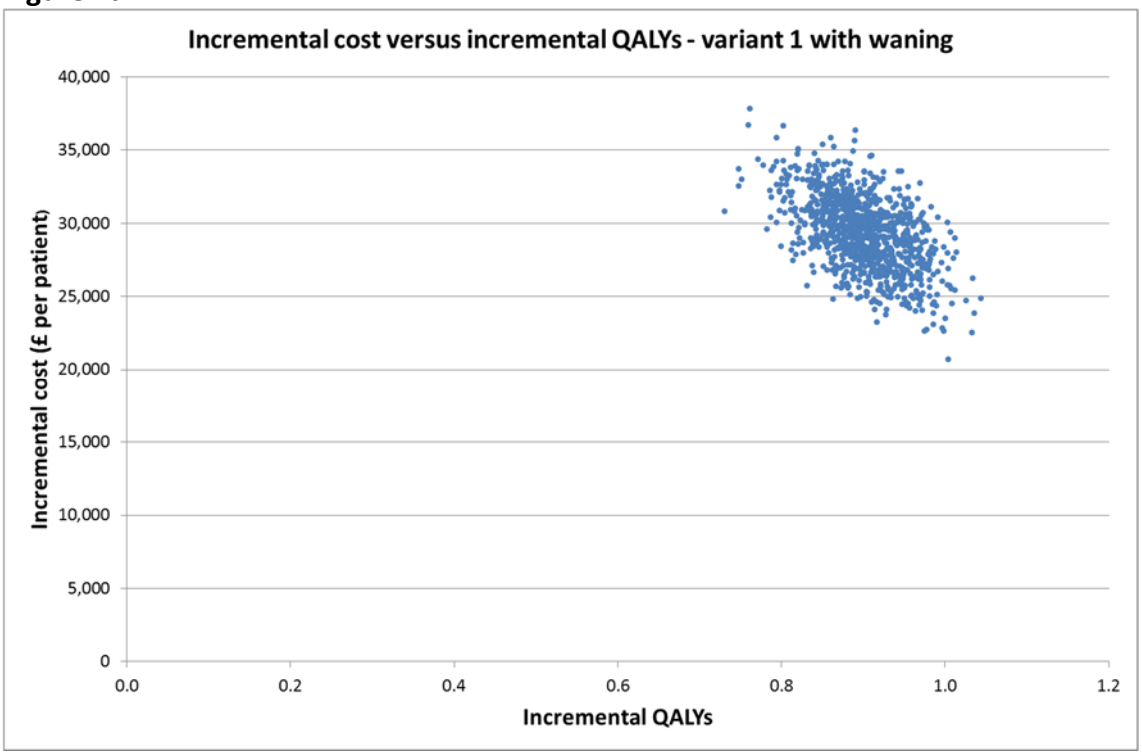


Figure 2b

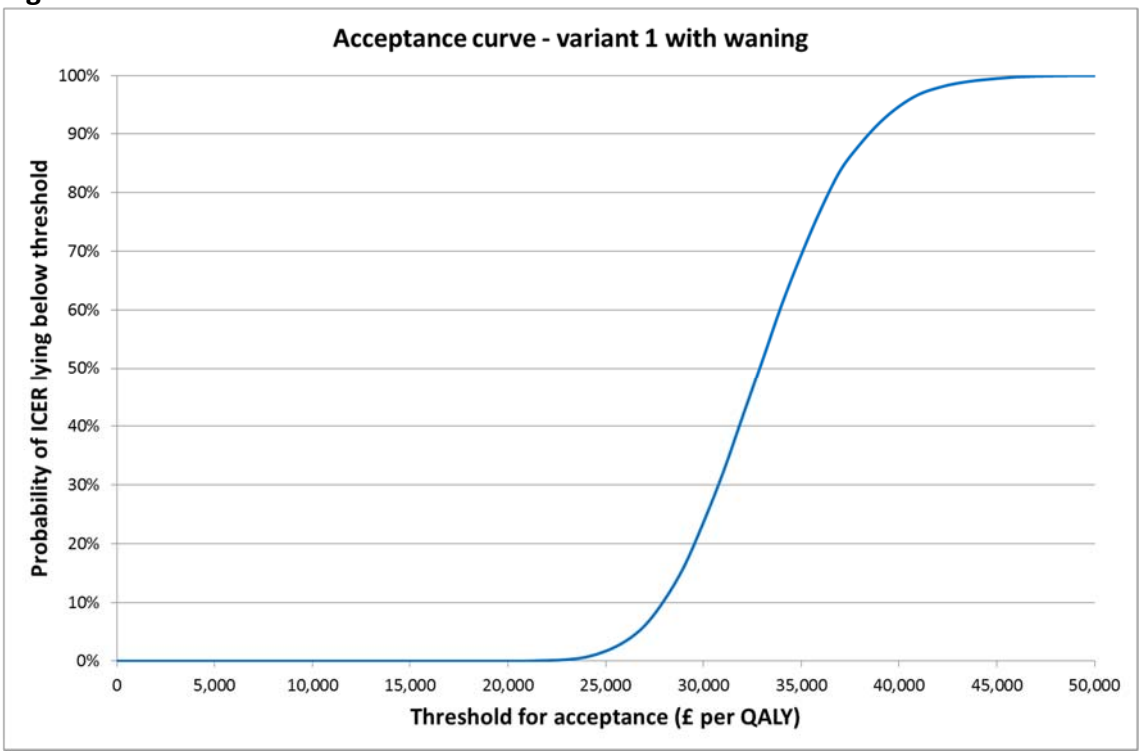


Figure 3: Scatterplot and acceptance curve for variant 3, without waning (10,000 samples)

Figure 3a

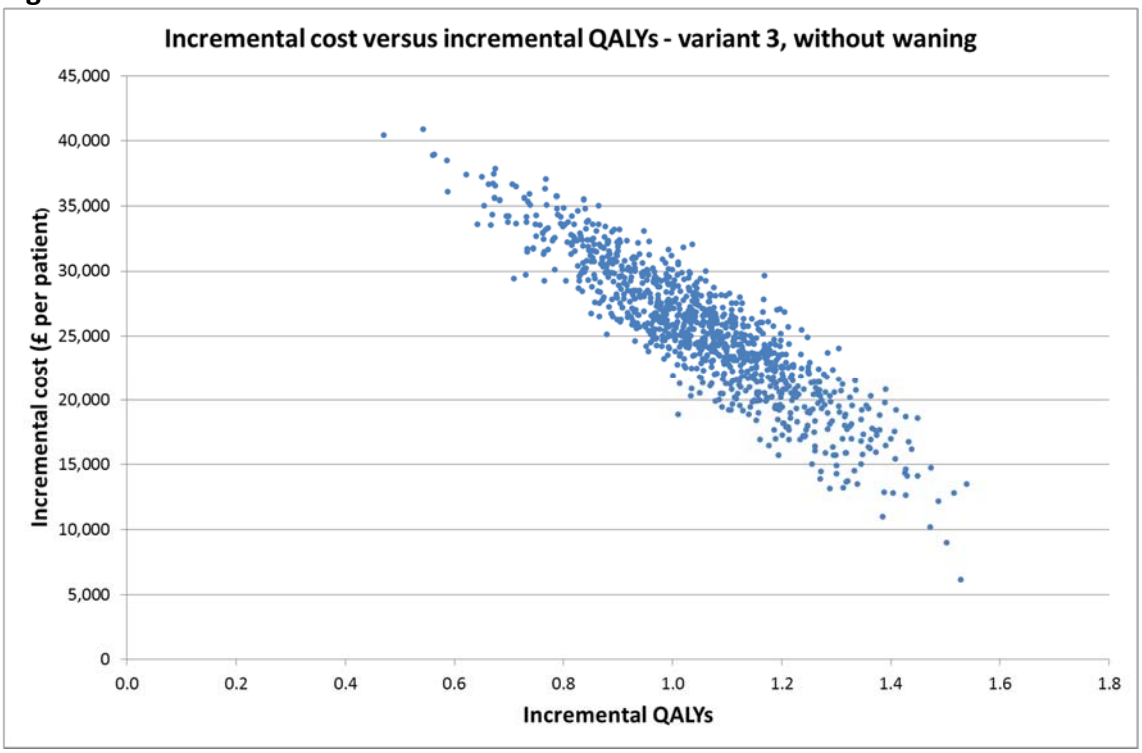


Figure 3b

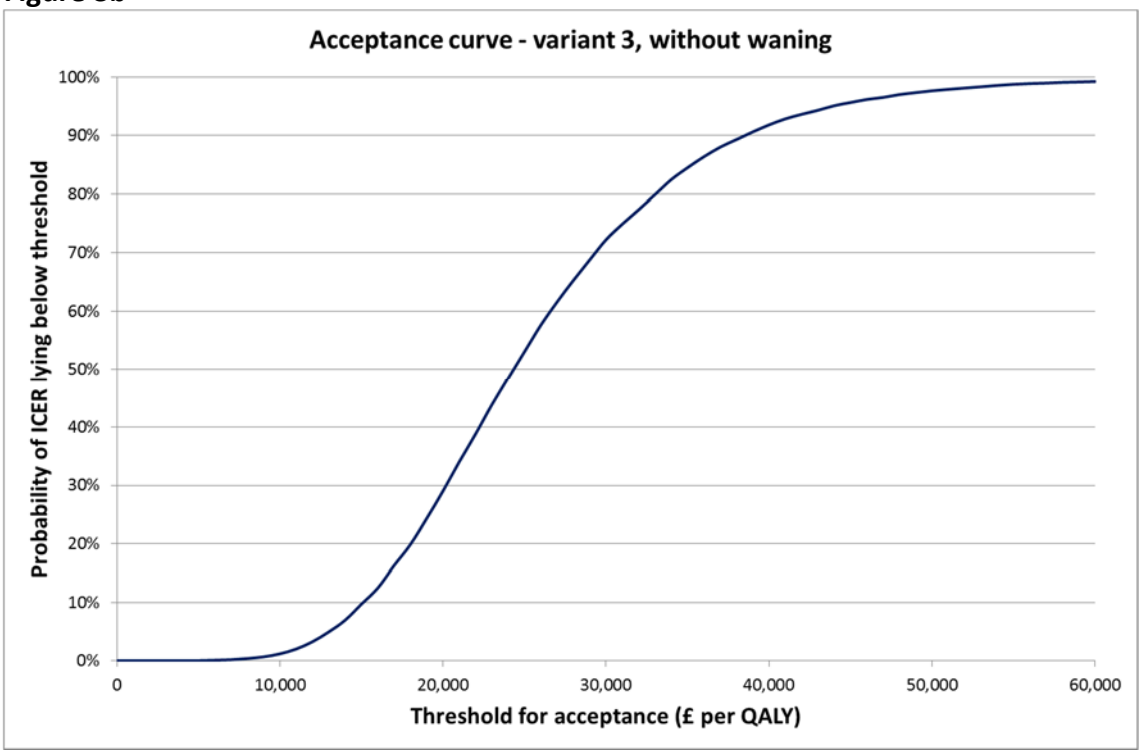


Figure 4: Scatterplot and acceptance curve for variant 3, with waning (10,000 samples)

Figure 4a

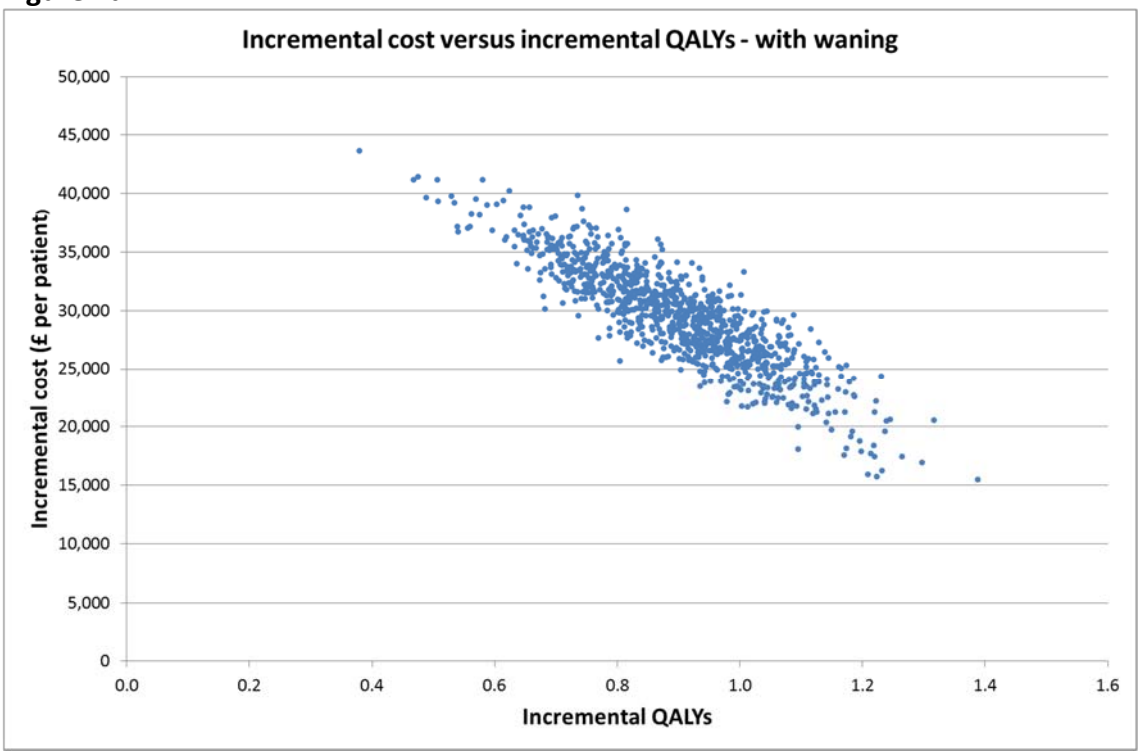
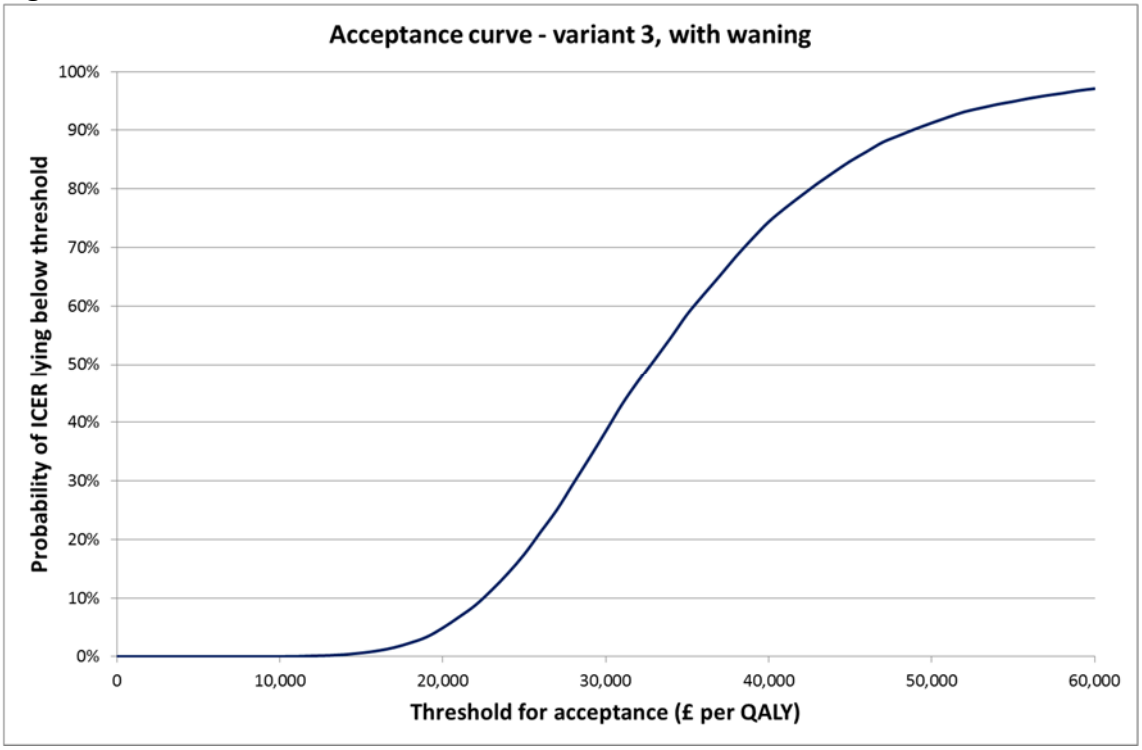


Figure 4b



APPENDIX 3: DETAILED COMMENTS ON THE ASSESSMENT GROUP'S REPORT

General

Throughout the report references are made to the "DH Risk Sharing Scheme". In fact the Scheme is sponsored by all UK Health Departments.

Abstract

Page 19, first para "Both RCT evidence and the DH RSS data are at high risk of bias": this seems a very sweeping statement and does not reflect the more nuanced discussion of possible sources of bias in the main report.

Main report

Table 22, page 198: we were slightly surprised to see the paper by Palace et al (*Lancet Neurology* 2015) included in the review of published cost effectiveness studies. Although the results reported in the paper (the 6-year follow up of the RSS cohort) do indeed have implications for cost effectiveness, the paper itself does not give a cost effectiveness estimate. The "RSS cost-effectiveness model", described in detail in chapter 13, is a related but separate model and results from this model have not so far been published.

Section 13.1, third para (p 205) "it was assumed that each year 5% of people would discontinue DMTs, and that this might be due to adverse events or progression to EDSS 7-9": not quite accurate – the model assumes a discontinuation rate of 5% pa for patients in EDSS 0 to 6, and <u>in addition</u> assumes that all patients reaching EDSS 7 or above discontinue treatment. The 5% assumption is based on an analysis of the 8-year follow-up data from the RSS.

Section 13.1, 4th para (p 205) "the analysis was undertaken from the UK NHS perspective in a primary care setting": we were rather puzzled by this statement. All patients in the RSS were initiated into care following an assessment with a specialist neurologist, and subsequent assessments also took place in the secondary care setting. A variety of arrangements are used, depending on the individual DMT, for day-to-day delivery of care to MS patients.

"The analysis was undertaken over a 50-year time horizon": our "base case" analysis, as agreed between the parties to the scheme, does indeed adopt a 50-year horizon, but should be noted that we also assumed a 50% reduction in the treatment effect (relative reduction in the rate of disease progression) after year 10 to allow for the very considerable uncertainties in projecting over such a long horizon. Without this assumption, we would recommend using a much shorter time horizon – the alternative version of the model we supplied to NICE, with a constant treatment effect, had a 20-year horizon.

Table 23 (p 206), "hazard ratio" row, "target outcomes were agreed for each of the 4 DMTs included in the RSS..": this confuses the two related Markov models used in the RSS. The "target outcomes" are used in the deviation model to assess whether the actual outcomes achieved by the DMTs over the 10 years of the scheme are in line with the "targets" agreed in 2002. For the cost effectiveness model, which is used to estimate new cost effective prices where indicated under the rules of the scheme, the hazard ratios (relative rates for forward transitions) were derived from the 10-year RSS data itself. See further below.

Table 23 (p 206), "base case analysis results"): we would regard the ICER of £33,700, using the version of the model with a time-varying treatment effect, as our "base case". On the alternative version of the model supplied to NICE (constant treatment effect and 20-year horizon) the ICER is £40,900.

Section 13.1.9 (p211) "it was not clear how these weighted averages were derived": the weights were the relative numbers of patients on the 5 treatments (including the two doses of Rebif) in the analysis cohort of the RSS. A similar weighted average approach was taken to other input parameters, eg the proportions of female to male and the relative relapse rate.

Section 13.1.10, 3rd para (p 211) "The assessment group believes that a systematic review could have been conducted to obtain more recent information on resource use": fair comment, but it should be noted that our general approach in the RSS was to stay with the assumptions originally agreed between the parties in 2002 unless there were strong reasons for making changes. There is a difficult trade-off in a risk-sharing scheme between stability, which reduces the risk to all parties, and making changes to reflect new scientific evidence. (This is a general issue for "commissioning by evaluation" for longer-term conditions, which we hope to pick up in dialogue with interested parties in reviewing the lessons from the RSS.)

Section 13.1.11, first para (p 212) " Additionally, the assessment group believes that a review of the literature could have been undertaken to obtain more recent information [on the cost of a relapse]": same comment applies.

Section 13.1.12 "health state utility values" (p 212): there is perhaps some slight confusion here. The "Boggild data set" was derived from RSS data (not from the original work by ScHARR) but, on advice from our Scientific Advisory Group, it was decided not to use it for the primary analysis of the year 6 and subsequent data. For our base run, therefore, we used the pooled data from the MS Trust and Heron datasets (the "2 pooled datasets"). The model provided to NICE also includes the facility to carry out sensitivity analyses using the Boggild dataset, either on its own or combined with the other two datasets (the "3 pooled datasets"). The sensitivity analyses we have carried out suggest that the choice between the "2 pooled" and "3 pooled" datasets is not critical.

Section 13.1.14 "treatment effect" (p 212): there are several misunderstandings in this para. Firstly, we did not derive estimates of the relative rate of relapse from RSS data – the assumptions were taken from the 2001 ScHARR model, based on the then

available RCT data. Secondly, the transition matrices for the "on treatment" cohort were not derived independently, but are obtained from the BCMS transition matrices by applying a hazard ratio for disease progression to all forward transitions (and assuming no effect on backward transitions). The hazard ratio is then varied by trial and error to obtain the same change in mean utility between baseline and year 10 as that actually observed in the RSS cohort. We call this the "implied hazard ratio" – for the DMTs in aggregate, this is the 0.7913 cited in this section. Thirdly, we do not assume that the hazard ratio for disease progression remains constant over the 50 year projection – in our base case we assume that the relative reduction reduces to 50% after year 10 (so the hazard rate to be applied from year 11 onwards is $1 – 0.5*(1 – 0.7913) = 0.8957$).

Section 13.1.15 "relapse frequency" (pp 213-214): the estimates of relapse frequency by EDSS state come from the 2001 ScHARR model. Estimates of the treatment effect of the individual DMTs (the relative rate of relapse) also come from the ScHARR model, based on data from the RCTs. These estimates are generally very close to those derived by the Assessment Group as reported in chapter 15.

Section 13.1.16 "treatment discontinuation" (p 214) "In the treatment arm of the economic model it was assumed that 5% of people discontinue treatment every year as a result of adverse events": the 5% is based on an analysis of the 8-year follow up data from the RSS. This is simply what we observed – no assumption is made about the reason for discontinuation of treatment. The analysis showed no obvious trend with time from baseline and only small differences between the individual DMTs.

"Additionally, it appears that people who discontinued treatment continued to accrue treatment benefits without additional costs": this is a misunderstanding. Within individual cycles, as a result of the "half-cycle correction" applied in this (as in standard Markov models), the effect is that patients received a further year of treatment benefit in the year in which they discontinue treatment, but only on average half a year of costs. In following cycles, both the costs and benefits of treatment cease and patients who have discontinued treatment follow the same trajectory as patients who have never been treated. Sensitivity analysis showed that the minor inconsistency in relation to the in-cycle effects has only a very small impact on the average ICER.

Section 13.1.18 "Time varying model" (p 215): it is perhaps worth emphasising that this "time varying model" (which uses different transition matrices for the first year after baseline and for subsequent years, in both the untreated and treated arms of the analysis) is different from the use of a time-varying treatment effect, ie the assumption referred to above that the treatment effect reduces to 50% of its value after year 10. Calculations with the time varying model gave a rather more favourable ICER than those of the base case.

Section 13.2 "Summary of critical appraisal of the RSS model" (p 215): see comments above on the 5% discontinuation assumption and the 72% relative relapse rate. In addition

"The assessment group noted that there was an increased risk of mortality for people with MS when compared to the general population, as well as transition probabilities to EDSS 10 (MS-related death). Using this assumption would lead to double-counting MS-related deaths in the model": not necessarily. Our understanding is that there is evidence that people with MS are at higher risk of death from non-MS causes in addition to a risk of death from MS-related causes. This is what we have attempted to model. However, our sensitivity analyses showed that this is not a critical assumptions – changing the SMR for general mortality from 2 to 1 reduces the ICER (on our base case estimates) from £33,700 to £33,000.

Section 14.1.19 (p 228) "In the [Biogen]model, people who progressed to a SPMS health state discontinued treatment": in the RSS cohort, the majority of patients who were assessed as switching to an SPMS state remained on their original DMT, at least for a period, even if the particular DMT was not licensed for use in SPMS. The clinical advisors to the RSS commented that the judgement on whether a patient had progressed to SPMS was quite subjective, and that clinicians often advised their patients to continue with active treatment until it was clear that they could obtain no further benefit. These considerations lay behind the advice of the RSS Scientific Advisory Group to drop the distinction between RRMS and SPMS in modelling disease progression for MS.

Table 60, first row "natural history cohort" (p 248): it's slightly misleading to say that the Teva natural history model is based on the London Ontario cohort – the probabilities for transitions between EDSS states are derived from the BCMS dataset and it is only the probabilities for transition between RRMS and SPMS states that come from London Ontario (via the 2001 ScHARR model).

Section 14.4.6, "Population studied" (p 254): "The assessment group consider that the age, sex and EDSS scores amongst those in the RSS dataset better reflect the UK RRMS population than participants recruited into a clinical trial": in general we agree, but there is some evidence that the patients recruited in the early years of the RSS may have contained a higher proportion of patients with long duration of disease at baseline (and therefore less potential to benefit from treatment) than a typical "incident" population. This would slightly bias the ICER against the DMTs. We provided evidence in this in the data supplied to NICE.

Section 14.4.7, first para (p 255) "Teva used the London Ontario data84 to derive the majority of their transition probabilities to model progression": see above.

"Transition probabilities: treatment effect", second para (p 255) "The relapse rates on DMTs obtained from the network meta-analysis tended to be lower that that obtained from the 10-year RSS datasets": we weren't quite sure whether this referred to the relapse rates for untreated patients or the relative relapse rates for treated patients. Either way, we are not aware of any use of the RSS dataset for this purpose. We suspect that the reference should be to the assumptions from the 2001 ScHARR model which we took over without change for the base case RSS model.

Third para (p 256) "A higher discontinuation rate will lead to lower lifetime costs but also lower quality adjusted years on DMTs. This may potentially impact on the ICER estimate": our sensitivity analyses show that a higher discontinuation rate results in a more favourable ICER, probably because the greatest benefits from treatment (in the model) are those accrued soon after baseline. Using a discontinuation rate of 2.9% (the Assessment Group's estimate based on RCT data) rather than our estimate of 5% (from 8-year RSS data) increases the ICER from £33,700 to £38,500.

Fourth para (p 256) "Not including a waning effect will not impact on lifetime costs on DMTs but will increase quality-adjusted years on DMTs, and likely result in lower ICER estimates." Actually there is an indirect effect on lifetime costs – assuming no waning results in slower progress to EDSS 7 (or to SPMS for models which make the distinction) and thus delays the point at which patients come off treatment. However, this increase in lifetime costs is greatly outweighed by the increase in QALYs so there is indeed a reduction in the ICER. On a 50-year horizon with our base case assumptions the ICER with "waning" is £33,700 compared to £25,300 without waning.

Section14.4.8, 3rd para (p 257) "The costs assigned to the EDSS states in Biogen's company submission tended to be lower than that used by Teva and Merck. This is likely to result in lower lifetime costs, but will affect both DMT and BSC strategies": yes, but there is a bigger effect on the BSC strategy because untreated patients reach these higher EDSS states sooner. Other things being equal, using the resource costs in the Biogen submission will result in a less favourable ICER than those using the RSS base case estimates.

Section 14.4.9, first para (p 257): the rather flatter curve of utility vs EDSS used by Biogen will result in a less favourable ICER.

Section 14.5.1 (p 261) "Teva used the London Ontario dataset in order to model disease progression": see comments above – Teva in fact used BCMS data as their main source of information on disease progression. Because of the redacted information we cannot comment at this stage on the differences between the Teva estimates and those of other companies, but see below for a query about the hazard ratio (apparently) supplied by Teva.

Section 5.1.4, para following table 64 (p 263): "Our combined annual probability of 2.29% is lower than the discontinuation rate assumed in the RSS model": we argue that the estimate derived from 8-year RSS data, representing normal clinical practice in the UK, is likely to be more robust than an estimate derived from short-term RCT data. If anything, our 5% estimate is likely to be an underestimate because we were not able to take account of patients discontinuing treatment after a switch to a non-scheme DMT (and also because we have evidence that patients who are lost to follow-up are more likely to have discontinued treatment than those who continue to be followed up).

"Discontinuation rates reported by each company, tended to be lower than those derived from our clinical review": table 64 appears to show the opposite.

Table 65 (p 264): The value of 0.6494 derived by the Assessment Group seems low compared with the spread of values for individual products given in the final column of the table – only Plegridy has a lower value (0.64) and the values for the other products are in the range 0.66 (Copaxone) to 0.80 (Avonex). I would expect an appropriately weighted average over the 5 products to be nearer 0.70, ie closer to the RSS value (which of course does not include a contribution from Plegridy).

Section "Treatment effectiveness: time to disability progression" (p 264) "The HR [from the Assessment Group's meta-analysis] was 0.6955 (95% CI [0.5530, 0.8747]). In contrast, the RSS model reported a reduced risk of sustained disease progression of HR 0.7913 (0.7705, 0.8122)": these two estimates are not comparable, for the reasons outlined in our covering note. In particular, it is not valid to take the hazard ratio of 0.6955, representing an estimate of the relative net rate of forward progression, and use it in a Markov model in which the hazard ratio is applied only to forward progressions and backward progressions are assumed to be unchanged.

Section "mortality" (p 265) "In the RSS model we noted that individuals were subject to MS-related mortality (modelled as twice the standardised mortality rate from other causes)..": see above – it is non-MS (general) mortality which is modelled as twice the rate as for the general population.

Section "resource use and costs" (p 266) "The costs of disease modifying treatments were obtained from the British National Formulary 2016": see covering note – this use of NHS list prices (instead of the "RSS prices" which will continue to be available to the NHS) will seriously affect the comparison between the 4 DMTs.

Section "Utility values, including carer disutilities" (p 266): "it appears that carers included in the analysis represent informal/unpaid carers. The NICE reference case suggests that the perspective should be all direct health effects, whether for patients or other people. Hence, the assessment group has excluded carers' disutilities from the main analysis": see covering note. We do not see the Assessment Group's logic – surely the disutility to a carer is a legitimate "direct health effect [on] other people"?

Section 15.1.5 (p 266) "We consider the RSS model base case with changes made to avoid double counting of mortality and removal of carer disutilities to be our base case": this statement slightly begs the question of what is the "RSS model base case". As noted above, we supplied NICE with two versions of the RSS model, one with a 50-year horizon and an explicit "waning" assumption (our preferred model, and the one agreed between the parties to the scheme) and one with no waning but a 20-year horizon. The Assessment Group's choice of a model with a 50-year horizon but no waning represents a further, very significant, change from the model supplied on behalf of the parties to the scheme and this should be explicitly recognised.

Table 60, "[relapse] rate ratio" (p 269): the confidence limits around the central value of 0.72 for the "RSS model" look very skewed (0.5262, 0.7623) compared to

the more or less symmetrical confidence limits around the alternative estimate of 0.6494 for the Assessment Group model (0.5572, 0.7567).

"Management costs" (p 269) and "Utilities" (p 270): it appears that, in the probabilisitic sensitivity analysis, the costs and utilities associated with each EDSS level are allowed to vary independently according to the specified distribution. This could have the paradoxical effect that, in some simulations, a patient moving to a higher EDSS level would incur lower costs and/or enjoy a higher utility as a result of the change in EDSS. Treatment, by slowing down the movement of patients to higher EDSS, would thus result in higher costs (in addition to the direct costs of treatment) and/or lower QALY gains. This appears to be the only plausible explanation for the otherwise incomprehensible finding that some replications have a negative QALY gain, ie appear in the "North west" quadrant of the cost vs QALY plot. I appreciate that this assumption of independent variation of each parameter is common in probabilitistic sensitivity analyses, but I would suggest caution so as not to over-interpret the results. An alternative approach is described in Appendix 2.

On a separate point, we were not quite clear how the AG applied the parameters derived from the ScHARR model in calculating the variation of the EDSS-specific utilities about the mean value from the pooled MS Trust/Heron datasets. In the ScHARR model, the distribution of each utility is described by a 3-parameter beta distribution, in which the "a" and "b" parameters have their usual function (defining the "tightness" and degree of skew of a distribution defined in the interval [0,1]) and the "c" parameter has the effect of stretching out the distribution into the interval [c,1]. c is given the value -0.594, representing presumably the worst possible state of health. The mean of the distribution is determined by a combination of all 3 parameters. Using the values in the ScHARR model the means approximate to the values used in ScHARR's deterministic analysis, but the variation about the mean is very wide – eg for EDSS 0 the 95% confidence intervals are (0.12, 0.98) about a mean of 0.68, and for EDSS 9 the CIs are (-0.59,+0.48) about a mean of -0.36. This variation about the mean is far wider than that found in the MS Trust and Heron datasets, and almost certainly accounts for the very wide variation in cost per QALY (and the replications in the "north west" quadrant, ie negative QALY gain and positive incremental cost) found in the AG's analysis. We would strongly recommend repeating the analysis with a distribution derived from the pooled MS Trust and Heron data – see Appendix 2 for details.

Tables 73-75 (pp 275-276): see covering note about the difficulty in making a fair comparison between Plegridy and the other products. Given this, it is unfortunate that the table presents the ICERs for the other products only versus Plegridy and not versus best supportive care. On a comparison against best supportive care, the ICERs for the individual products (excluding Plegridy) are in the range £14,000 to £26,000 for sensitivity analysis S2A, and £5,000 to £17,000 for analysis S2B. These figures presumably underlie the Assessment Group's conclusion in the abstract (not otherwise apparently evidenced) that the "DMTs *both separately* [our emphasis] and together are clinically and cost effective for treatment of … RRMS".

Table 75 (p 276): we were puzzled at the figures given for Copaxone, which would imply an ICER versus best supportive care of £33,400. We do not know the exact assumptions used by the Assessment Group since these are redacted in Table 70. However, an ICER of this order of magnitude would require a relative hazard ratio for forward progression of around 83% which is much higher than the "implied hazard ratio" arising from the RSS year 10 analysis. The calculations in SA3 for both Avonex and Rebif appear to use the expected value of the implied hazard ratio. We therefore suggest that, for a fair comparison, Copaxone should be assessed on the same basis. This would result in an ICER of the order of £12,200.

Section "SA5: parameter uncertainty analysis" and Figures 26-27 (pp 278-279), "The model remained robust to changes to the treatment discontinuation rate and the model time horizon": this conclusion needs to be considered in relation to the size of the parameter variation adopted. For the discontinuation rate, a variation of ±10% means (presumably) a variation of between 2.7% and 3.1% about the AG's preferred value of 2.9%. This does not seem an adequate range given the difference between the AG's value, the value based on RSS data (5%) and the values submitted by the companies (up to 10.4% according to table 70). With a wider range of variation, this parameter makes a significant contribution to the overall uncertainty, though not as much as the other parameters considered by the AG. Similarly for the time horizon it is hardly surprising that a variation between 46 years and 54 years makes little difference, given that both costs and QALYs are discounted at 3.5%. On the contrary, adopting a time horizon of 20 or 30 years makes a considerable difference. (The AG present calculations for individual DMTs for these shorter horizons, but not for the DMTs in aggregate.)

Figure 29 (p 280): the acceptability curve seems very flat, and the finding that only 37% of the simulations achieved a cost per QALY of £20,000 or less must be some cause for concern (and slightly undermines the assertion in the abstract that the DMTs in aggregate are clearly cost effective). It is unfortunate that the AG did not examine more critically the assumptions which led to this finding. If it is driven by the assumptions on cost and utility as a function of EDSS (see above) then in my view figure 29 will greatly exaggerate the variation of the cost per QALY about the mean value given by the deterministic analysis.

Section 15.3.2 "Strengths and weaknesses", second para (p 283) "in particular, we did not have a confidence interval for the annualised relapse rate": a confidence interval was available in the 2001 ScHARR model from which this parameter was drawn. In any case, the sensitivity analysis reported in figures 26 and 27 shows that the ICER is not very sensitive to this particular parameter. We suggest that the lack of this particular confidence interval is hardly a major "weakness" of the analysis.

DH estimates of cost-effectiveness ratios using the RSS model and year 10 data[a]

A. Using transparent NHS prices

DMT	Without "waning"			With "waning"		
	Net cost (£)	Net QALYs	ICER (£ per QALY)	Net cost (£)	Net QALYs	ICER (£ per QALY)
All RSS DMTs	31,684	1.047	30,262	35,695	0.900	39,648
Avonex	[redacted]					
Betaferon	[redacted]					
Rebif	[redacted]					
Copaxone	[redacted]					

1. NHS list prices for Avonex (£8,502 per patient per year), Betaferon (£7,259) and Copaxone (£6,701); RSS price as published in 2002 Health Service Circular for Rebif (Rebif 22 [redacted], Rebif 44 [redacted]). The incremental costs and benefits for the two doses of Rebif are combined in proportion to the number of patients on each dose in the RSS cohort. The weighted average over all 4 products is approximately £8,000 per patient per year.
2. Other assumptions as in the DH comments on the Assessment Group's report.
3. In calculating the ICERs for DMTs in aggregate, all available data are used including data after patients switch to another DMT; for individual products, data after such switches are excluded. The calculations for individual products are therefore more directly comparable to those in variant C1b below.

B. Prices as for (A), Assessment Group modifications to the RSS model

DMT	Without "waning"			With "waning"		
	Net cost (£)	Net QALYs	ICER (£ per QALY)	Net cost (£)	Net QALYs	ICER (£ per QALY)
All RSS DMTs	31,838	0.943	33,748	35,845	0.812	44,151
Avonex	[redacted]					
Betaferon	[redacted]					
Rebif	[redacted]					
Copaxone	[redacted]					

1. The changes from (A) are (a) carer utilities are excluded, (b) the product-specific discontinuation rates estimated by the Assessment Group are used in place of the common assumption of a 5% discontinuation rate derived from the RSS year 8 data.
2. In estimating the ICER for the DMTs in aggregate, an average price of £8,000 per patient per year has been used as in (A). The Assessment Group used a rather lower figure (£7,300) which represents the weighted average of the net NHS costs as at year 8, including discounts and contributions to NHS infrastructure costs. Using this

lower average price we calculate an ICER of £25,627 without waning (in good agreement with the AG's £25,600) and £29,723 with waning.

[redacted]

Variant	Without "waning"			With "waning"		
	Net cost (£)	Net QALYs	ICER (£ per QALY)	Net cost (£)	Net QALYs	ICER (£ per QALY)
Base run	31,684	1.047	30,262	35,695	0.900	39,648
C1a	29,998	1.113	26,956	34,303	0.955	35,921
C1b	28,197	1.183	23,830	32,821	1.013	32,392
C2	31,894	1.039	30,702	35,868	0.893	40,144
C3a	29,645	1.026	28,902	34,327	0.875	39,239
C3b	32,528	1.042	31,202	36,345	0.898	40,464
C4	23,095	1.309	17,643	28,334	1.120	25,308

Variant C1a: excluding data after patients have switched to a non-scheme DMT.
Variant C1b: excluding data after patients have switched to any other DMT.
Variant C2: missing data in the RSS imputed using the multilevel model to project forward from the available data for each patient.
Variant C3a: assumes that DMTs reduce the rate of backward transitions in the same proportion as for forward transitions [nb in the base run it is assumed that DMTs have no effect on the rate of backward transitions]
Variant C3b: assumes that DMTs increase the rate of backward transitions in inverse proportion to the effect on forward transitions.
Variant C4: using transition matrices augmented to adjust for missing data in the BCMS dataset.

D. Probabilistic sensitivity analysis – acceptance curve for run (A)

Threshold (cost per QALY)	Probability of an ICER equal to or lower than threshold:	
	Without waning	With waning
£20,000	9.0%	1.0
£25,000	28.0%	3.8
£30,000	46.0%	14.2
£36,000*	66.0%	37.4
£40,000	79.7%	52.8
£45,000	87.0%	71.1
£50,000	93.0%	82.0

*Threshold agreed for the purpose of the 2002 Risk Sharing Scheme

Comments provided to Healthcare Improvement Scotland by:

[redacted]

NICE MTA: Beta interferon and glatiramer acetate for multiple sclerosis (Review of TA 32)
ASSESSMENT REPORT FOR CONSULTATION

SUMMARY

Authors performed a systematic review of clinical and cost effectiveness of classical first line disease modifying therapies (DMTs) in relapsing remitting multiple sclerosis (RRMS), secondary progressive MS and clinically isolated syndrome (CIS). DMTs were compared against best supportive care and each other. Annualised relapse rate (ARR) and to progression at 3 months and 6 months were the main outcomes.
Authors evaluated 35 randomized clinical trials. The main findings is there was very little difference between the analyzed DMTs in reducing moderate or severe relapse rates in relapsing remitting MS, and all these drugs were beneficial against best supportive care. In their analysis, authors concluded that glatiramer acetate 20 mg sc had the "highest probability" of being the best in reducing annual relapses rates followed by Pegylated IFN B-1a. Interferon (IFN) B-1a had the "highest probability" of being the most effective. Pegylated IFN B-1a was the most cost effective DMT and glatiramer acetate was the most cost-effective treatment for CIS. However I believe that there are no significant differences regarding outcomes when comparing all first line treatments in RRMS.
The final conclusion is that beta interferons and glatiramer acetate are cost effective for the treatment of both, relapsing remitting MS and CIS. In addition the supportive evidence may be at high risk of bias; for this reason authors suggested comparative studies with longer follow up and systematic reviews and meta-synthesis of qualitative studies.

REPORT

This is a nice and well written, high quality, review. I believe that there is no outstanding omission of relevant data from literature.
Authors performed a deep, evidence-based, review of the evidence available for the use of beta interferon and glatiramer acetate in RRMS and CIS. These DMTs have been used in the prevention of relapses in RRMS for almost 20 years and have been considered the first line treatment. There is a lot of information regarding tolerability, side effects and safety risk stratification in the literature. As most of patients are females, the concern with pregnancy is a fact that should be included in the analysis. We know that glatiramer acetate is the safest drug to be used in young females who want to become pregnant in the future. In addition its profile of better tolerability, as compared to beta interferons, makes this drug one of the drugs of choice as a first line in moderate active RRMS. We have also long-term data in the literature regarding the efficacy of IFN B-1a and IFN B-1b and glatiramer acetate for the prevention of relapses, and the level of efficacy of all these drugs seems to be similar. More data and analysis is required regarding Pegylated IFN B-1a.
I feel that the data about long-term efficacy regarding prevention of disability progression is indeed limited. Most of studies have focused on "time to progression at 3 and 6 months". This outcome seems to be insufficient when considering the progression of disability in the long-term in multiple sclerosis patients. In addition,

many patients evaluated for progression at 3 or 6 months may be indeed under the effect of previous sequel disability caused by a recent relapse. There are no good quality studies that have evaluated the long term effect of glatiramer acetate or beta interferons on cognitive function and/or brain atrophy. So we have to recognize that the existing data about the use of DMT (beta interferons and glatiramer acetate) have focused on short-term outcomes (annualized relapse rate and short-term disability progression), and that the knowledge and data regarding the long-term effect for these drugs are limited.

Other methodological limitation of the analyses is the fact that populations are not comparable. Inclusion criteria used in the randomized clinical trials changed in the last 20 years, from Poser criteria, MacDonald criteria 2001, 2005 and 2010. In addition, it may be difficult to compare relapse frequency and natural history between contemporary patients diagnosed as having clinically definitive MS based on MacDonald 2010 criteria, a single first ever relapse plus contrast-enhancement plaques on MRI, from those who were recruited in the initial historical beta-interferon clinical trials based on “history of at least 2 relapses in the last 2-3 years”. I wonder if British Columbia historical series used in the Risk Shared Scheme may have a more severe form of MS when compared with the diagnosis done recently in the last years with new onset or naive patients presenting with early MS diagnosis. This fact could have an influence to the cost-effectiveness data.

The field of multiple sclerosis is changing rapidly. We have now twelve different medications available including the new oral treatments used as a first line DMT (teriflunamide, dymethil fumarate), new formulations (glatiramer acetate 40 mg; possible generic medications), and other drugs used for highly active MS (natalizumab, fingolimod, alemtuzumab). In addition, it is expected that several new drugs (ocrelizumab, daclizumab, laquinimod, cladribine, among others) may appear in the market in the next few years. For this reason, there is an urgent need to establish treatment algorithms for RRMS.

In addition, we need comparative clinical studies to compare efficacy, safety, effectiveness between classical first line treatments (beta interferons, glatiramer acetate) and the new oral treatments (dymethyl fumarate and teriflunamide). Outcomes to be analyzed should include annualized relapse rate, long-term disability prevention, and cognition measures (clinical and radiological markers of brain atrophy).

There are other variables that need to be taken into account in the “real world”, outside from evidence-based medicine, when considering the choice or election of a first line treatment for prevention of relapses in RRMS: patient’s values and preferences, and a well informed balance between efficacy and safety (risk of serious adverse effects) should be taken into account. “Needle phobia” and “needle fatigue” are important issues when considering long-term adherence to injectables or oral first line treatments in MS. For this reason, a proper algorithm and also a formal review in the future of oral versus injectable first DMTs in RRS would be advisable.

Another point to be considered in the future is the possibility of switching to new formulations of glatiramer acetate. Authors found that glatiramer acetate was the most effective in reducing annualised relapse arte in RRMS. However many patients are willing to use 40 mg three times a week instead of daily formualtions; could have this an impact on this data and outcomes?; are there any available data regarding long-term prevention of relapses rates and disability progression with this new 40 mg glatiramer acetate formulation?

Authors evaluated the research priorities in this report. They recognized that one key flaw in the analysis of clinical effectiveness evidence is the lack of long-term follow-up studies, and this is another important point to be taken into account.

In summary, this is a good quality meta-analysis regarding beta interferons and glatiramer acetate in RRMS.

WARWICK EVIDENCE response to consultation comments

1. Comments from DoH

3. Our main concerns are as follows:

i Relative rates of disease progression. For the calculations on individual DMTs (AG calculations SA2a and SA2b, and the calculation for Plegridy in SA3) the AG has used relative hazard rates for disease progression derived from RCT data as a direct input to the RSS model. Unfortunately, this is not valid. The reasons are set out in detail in an Annex to the report on the year 6 analysis by the RSS Scientific Advisory Group which formed part of the documentation supplied to NICE (see attached extract at Appendix 1). In brief the use of hazard rates for (net) forward disease progression will give an exaggerated impression of the effect of DMTs in slowing disease progression when used in a model which assumes that "backward" transitions (disease regression) are unaffected by treatment.

In our view, the most robust way of estimating the effects of individual DMTs on disease progression would be to use the "implied hazard ratios" derived from 10-year RSS data for individual products (comparable to the hazard ratio of 0.7913 for the DMTs in aggregate which the AG have adopted for their base run). These implied hazard ratios will have been supplied by the individual companies as part of their submissions to NICE and appear to be the basis for the parameters used for Avonex and Rebif 44 in AG calculations SA3.

→ AG response:

As we stated in our report and as reflected in our choice of the AG Base Case, we believe that it is reasonable to use hazard ratios derived from the 10 year-RSS data.

The RSS hazard ratios are likely to be more robust than our Sensitivity Analysis 2 (SA2). SA2 which was based on our own detailed systematic reviews informing network meta-analysis (NMA) of the published RCT data.

We agree that the limited sample size and follow-up of published RCTs mean that the confidence intervals around estimates in the NMA are wide (they include the company-submitted values), and may over-estimate medium and long term effects of treatment.

We do not accept however that the approach in SA2 is invalid based on the material included in Appendix 1. The appendix sets out how the target forward transition probability ratio needs to be adjusted when moving from a model that does not allow backward transitions to one that does, in order to arrive at the same target change in mean EDSS score. This is not relevant to the application of empirical hazard ratios to transition matrices estimated from observed data. We believe that our method is consistent with method 2 as described in Appendix 1 of the documentation supplied to NICE in the DH response, as we have applied the hazard ratio to forward transitions while assuming backward transition hazards are unaffected.

One of the main problems was that we were unable to undertake analyses based on hazard ratios derived from the 10 year-RSS data for individual products, because we were not provided with the appropriate individual product hazard ratios by the DH

We therefore conducted an analysis based on the *company-submitted* hazard ratios which were available to us (only provided by some of the companies). And only some (but not all) of these hazard ratios were based on RSS data.

As the DH acknowledge, this is the basis of SA3 which we undertook. Hazard ratios based on the RSS were only available for 3 of the 5 DMTs from the NICE scope (pegylated IFN was not in the RSS and a company submission was not provided for IFN beta 1-b). We therefore stand by our decision, given the information available to us at the time, to explore the impact of using hazard ratios based on our systematic review of RCT evidence in SA2.

The approach we took, based on our own NMA of published RCT data, was the only option available to us to allow comparison of the DMTs included in the scope with each other (as outlined in the scope) in order to allow ranking of individual DMTs according to their cost-effectiveness.

(There appears to be a problem with Copaxone where the results reported in table 75 are much less favourable to the product than we would have expected.)

→ AG response: Thank you for highlighting this. We have corrected it and the analysis can be found in the erratum submitted to NICE (1).

We appreciate that there is an issue with Plegridy, where 10-year follow-up data from the RSS are not available. From the evidence presented by the AG Plegridy appears to have a greater treatment effect in the short term than other interferon beta 1a preparations such as Avonex, but it would be hazardous to assume that this will remain true over longer periods. There is no obvious solution to this dilemma, but we do suggest that the estimates presented by the AG for Plegridy should be treated with considerable caution, and in particular that the cost-effectiveness of the other DMTs should be assessed against best supportive care rather than against Plegridy (as the apparently cheapest treatment option).

→ AG response: We have noted this.

ii Carer disutilities. The AG have not included carer disutilities in their base run, although they do include them in a sensitivity analysis in an appendix. Our understanding is that there is precedent for including carer disutilities in the base run in other NICE appraisals, eg the appraisal of Natulizumab. We consider that, for a long-term condition in which patients are likely to need considerable help from informal carers for substantial periods of their life, it would be reasonable to include the quality of life impact on carers as part of the assessment.

→ AG response: We note this. We have undertaken an additional analysis which includes the waning effect and carers' disutilities (SA6) (2, 3). Our view is that there is a lack of consensus on the inclusion of carers' disutilities in the NICE reference case, which is why we excluded it in our base case. In the NICE Natalizumab appraisal TA127(4), the ERG noted 'Care giver disutility included in base case analysis for NHS & PSS perspective. This may not be appropriate for NICE reference case' (page 60 and section 5.4). As the DH recognise, we included sensitivity analyses using carers' disutilities in our original report. The results suggested that the cost-effectiveness of the interventions is not sensitive to the inclusion/exclusion of carers' disutilities.

iii Discontinuation rates. The AG rightly draw attention to the potential impact of discontinuation rates on estimates of cost-effectiveness. (Perhaps paradoxically, a higher discontinuation rate in the RSS model results in better cost effectiveness – lower cost per QALY – though this may well be an artefact of the model assumptions.) However, their report does not make clear that the assumption of a 5% discontinuation rate included in the RSS model (and in the AG's base case) is derived from RSS data, reflecting long-term follow-up of patients under "normal" clinical conditions, rather than an arbitrary assumption. Our analysis also showed that there are only very small differences in the discontinuation rates between the 4 DMTs in the RSS. We consider that, in comparing the cost effectiveness of individual DMTs, it would be more robust to use a common assumption of a 5% discontinuation rate rather than the very different estimates derived from the individual RCTs.

→ AG response: This is noted. We will amend this in the final version of our report.

Iv DMT acquisition costs. For two of the 4 DMTs in the RSS, NHS patients will for the foreseeable future be able to access the drugs at a lower effective price than the NHS list price, through arrangements comparable to a patient access scheme. Details of these arrangements will have been supplied to NICE in the relevant company submissions. In one case, the discount below NHS list price is very significant. We will be responding separately to a query from the NICE's Programme Director about the status of these "effective NHS prices", but there is a case for saying that they should be used, rather than the NHS list prices, in order to give a fair comparison of the cost effectiveness of the 4 products.

→ AG response: Additional analyses using price discounts and infrastructure contributions provided by each company have been performed and sent to NICE as Addendum 1 and 2. (2, 5).

v Rebif. For Rebif, two doses (22 mcg and 44 mcg) are licensed for use in the UK. The AG group have only considered the cost-effectiveness of Rebif 44, but the evidence from the RSS shows that a substantial proportion of patients (about one-third) remain on or are titrated down to the lower dose. We consider that this should be taken into account to give a fair comparison between Rebif, as used in normal UK clinical practice, and the other DMTs.

→ AG response: We have also undertaken analyses with an adjusted cost, based on this information. These have been submitted to NICE (2, 3).

vi Handling uncertainty over long-term treatment effects ("waning"). The AG's base case uses a 50-year horizon (in effect, a lifetime horizon) in line with NICE guidance that the time horizon should reflect the long-term effects of treatment. We agree that this is entirely appropriate. However, even using RSS data we only have evidence on the treatment effects of the DMTs for 10 years. To reflect uncertainty over the treatment effect for the much longer periods involved in modelling, the parties to the RSS agreed that it would be reasonable to apply a 50% reduction to the effect of treatments on disease progression after year 10 of the projection. This is in line with precedents from other NICE appraisals where long-term effects have to be extrapolated from shorter-term data, eg the appraisal of natulizumab[i].

This "waning assumption" is referred to in the AG's chapter 14 (the critique of the company submissions) but is not discussed at all in chapter 15 (the AG's base case and sensitivity

calculations). We consider that the Appraisal Committee should have access to calculations of cost effectiveness both with and without "waning", both for the DMTs in aggregate and for individual DMTs.

→ AG response: We note this. We have undertaken additional analyses which include the waning effect, both with and without carers' disutilities (SA6) and have also included a PSA where we assume a waning effect (2, 3).

vii Baseline EDSS distributions. The cost-effectiveness of treatment is sensitive to the assumption made about the distribution of patients over EDSS states at the start of treatment (the "baseline EDSS distribution"). Broadly, the higher the proportion of patients in higher EDSS states, the less the opportunity to benefit from treatment and the less favourable the cost-effectiveness ratio. In the RSS, we noted some differences in the baseline EDSS distributions for the different DMTs and we used product-specific distributions in the price adjustment calculations specified by the scheme. However, we agree with the AG's implicit assumption in the calculations presented in chapter 15 that the <u>same</u> distribution should be used for each DMT in order to allow a like for like comparison.

→ AG response: Thank you for this acknowledgement of our assumption that the same distribution should be used for each DMT. This allows a fair, like for like comparison.

viii Probabilistic sensitivity analysis. We were surprised at the AG's finding that a number of replications showed treatment to be dominated by best supportive care (higher cost and lower QALYs). On investigation, we believe this is due to a combination of two factors: (a) use of the very wide confidence intervals on the utility associated with different EDSS states taken from the 2001 ScHARR model, (b) the assumption that each of these utility values can vary independently around its central value. Taken together, these assumptions lead to the implausible result that in some replications a patient can move to a better quality of life (higher utility) as a result of moving up one or more EDSS levels. In addition, use of these (in our view) extreme assumptions results in exaggerating the dispersal of the resulting cost per QALY about its central value and thus, other things being equal, an underestimate of the probability of achieving any likely cost per QALY threshold.

→ AG response:

We have reviewed the distributions used for utility values in light of the very recent additional information now provided to us by the DoH in their response. The revised distributions are less dispersed, and as a result, we no longer find any replications in which treatment is dominated by best supportive care (1). We agree that it would be appropriate to use a joint multivariate distribution for utility values, but we were not provided with the covariance values required to do this. With the revised distributions, the impact of not including correlations will be reduced.

4. With the modifications discussed above, but otherwise accepting the AG's preferred assumptions (mortality, relative rate of relapse, same baseline EDSS distribution for each product) our calculations of the ICER for the DMTs in aggregate and for the 4 products in the RSS, with and without waning, are as below:

DH estimates of cost-effectiveness ratios using the RSS model and year 10 data

DMT	*Without "waning"*			*With "waning"*		
	Net cost (£)	*Net QALYs*	*ICER (£ per QALY)*	*Net cost (£)*	*Net QALYs*	*ICER (£ per QALY)*
All RSS DMTs[b]	*25,473*	*1.047*	*24,329*	*29,572*	*0.900*	*32,847*
Avonex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Betaferon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rebif[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Copaxone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a. Final net RSS prices; "implied hazard ratios" and discontinuation rates from the year 10 RSS data; relative relapse rates from the AG; including carer disutilities; SMR for general mortality = 1 as in the AG's base case

b. Weighted average of all DMTs in the RSS, using the relative proportions in the RSS cohort as the weights

c. Weighted average of estimates for Rebif 22 and Rebif 44, using the relative proportions in the RSS cohort as the weights

→ AG response: These results have been noted and our results (where it is possible to calculate them from the data available) are included in the table alongside these (see table 1). Analyses include list prices, 5% discontinuation rates, companies' implied hazard ratios, carers' disutilities and SMR = 1. Our results are in line with those of the DH, apart from the incremental costs for Rebif. In this analysis, we used the weighted average estimates for Rebif (22mcg and 44mcg). However, it appears from the DH analysis that a different (greater) weight must have been placed on Rebif (22mcg). It would be unwise for us to speculate on the reason for this since the underlying data have not been provided to us, but perhaps this reflects the composition of use in the RSS cohort.

Table 1: DH and AG estimates of cost-effectiveness ratios using the RSS model and year 10 data[a]

DMT	Without "waning"						With "waning"					
	DH	AG	DH	AG	DH	AG	DH	AG	DH	AG	DH	AG
	Net cost (£)	Net cost (£)	Net QALYs	Net QALYs	ICER (£ per QALY)	ICER (£ per QALY)	Net cost (£)	Net cost (£)	Net QALYs	Net QALYs	ICER (£ per QALY)	ICER (£ per QALY)
All RSS DMTs	25,473	25,600	1.047	1.046	24,329	24,500	29,572	29,700	0.900	0.899	32,847	33,100
IFN β-1a 30µg IM once weekly (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1b 250 µg every other day (Betaferon)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44µg SC three times a week (Rebif)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg daily (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5. Using these modifications and the additional assumptions set out in Appendix 2, our estimates of the probability of achieving various cost-effectiveness thresholds for the DMTs in aggregate are as follows:

Threshold (cost per QALY)	*Probability of an ICER equal to or lower than threshold:*	
	Without waning	*With waning*
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

**Threshold agreed for the purpose of the 2002 Risk Sharing Scheme*

→ AG response: These results have been noted.

*6. **DETAILED COMMENTS ON THE ASSESSMENT GROUP'S REPORT***

General

Throughout the report references are made to the "DH Risk Sharing Scheme". In fact the Scheme is sponsored by all UK Health Departments.

→ AG response: We have noted this and will amend the reference in our final version.

Abstract

Page 19, first para "Both RCT evidence and the DH RSS data are at high risk of bias": this seems a very sweeping statement and does not reflect the more nuanced discussion of possible sources of bias in the main report.

→ AG response: We have noted this.

Main report

Table 22, page 198: we were slightly surprised to see the paper by Palace et al (Lancet Neurology 2015) included in the review of published cost effectiveness studies. Although the results reported in the paper (the 6-year follow up of the RSS cohort) do indeed have implications for cost effectiveness, the paper itself does not give a cost effectiveness estimate. The "RSS cost-effectiveness model", described in detail in chapter 13, is a related but separate model and results from this model have not so far been published.

→ AG response: We agree there was an error in the referencing. The review related to Palace et al, 2014 BMJ Open (6).

Section 13.1, third para (p 205) "it was assumed that each year 5% of people would discontinue DMTs, and that this might be due to adverse events or progression to EDSS 7-9": not quite accurate – the model assumes a discontinuation rate of 5% pa for patients in EDSS 0 to 6, and in addition assumes that all patients reaching EDSS 7 or above discontinue treatment. The 5% assumption is based on an analysis of the 8-year follow-up data from the RSS.

→ AG response: We will amend in the final report so that it accurately reflects this statement.

Section 13.1, 4th para (p 205) "the analysis was undertaken from the UK NHS perspective in a primary care setting": we were rather puzzled by this statement. All patients in the RSS were initiated into care following an assessment with a specialist neurologist, and subsequent assessments also took place in the secondary care setting. A variety of arrangements are used, depending on the individual DMT, for day-to-day delivery of care to MS patients.

→ AG response: This was an error and should have read

"the analysis was undertaken from the UK NHS and PSS perspective"

"The analysis was undertaken over a 50-year time horizon": our "base case" analysis, as agreed between the parties to the scheme, does indeed adopt a 50-year horizon, but should be noted that we also assumed a 50% reduction in the treatment effect (relative reduction in the rate of disease progression) after year 10 to allow for the very considerable uncertainties in projecting over such a long horizon. Without this assumption, we would recommend using a much shorter time horizon – the alternative version of the model we supplied to NICE, with a constant treatment effect, had a 20-year horizon.

→ AG response: We have now undertaken a sensitivity analysis on our base case where the time horizon is reduced to 20 years and submitted this to NICE (3).

Table 23 (p 206), "hazard ratio" row, "target outcomes were agreed for each of the 4 DMTs included in the RSS..": this confuses the two related Markov models used in the RSS. The "target outcomes" are used in the deviation model to assess whether the actual outcomes achieved by the DMTs over the 10 years of the scheme are in line with the "targets" agreed in 2002. For the cost effectiveness model, which is used to

estimate new cost effective prices where indicated under the rules of the scheme, the hazard ratios (relative rates for forward transitions) were derived from the 10-year RSS data itself. See further below.

→ AG response: We have noted this.

Table 23 (p 206), "base case analysis results"): we would regard the ICER of £33,700, using the version of the model with a time-varying treatment effect, as our "base case". On the alternative version of the model supplied to NICE (constant treatment effect and 20-year horizon) the ICER is £40,900.

→ AG response: We have noted this.

Section 13.1.9 (p211) "it was not clear how these weighted averages were derived": the weights were the relative numbers of patients on the 5 treatments (including the two doses of Rebif) in the analysis cohort of the RSS. A similar weighted average approach was taken to other input parameters, eg the proportions of female to male and the relative relapse rate.

→ AG response: Thank you for explaining this.

Section 13.1.10, 3rd para (p 211) "The assessment group believes that a systematic review could have been conducted to obtain more recent information on resource use": fair comment, but it should be noted that our general approach in the RSS was to stay with the assumptions originally agreed between the parties in 2002 unless there were strong reasons for making changes. There is a difficult trade-off in a risk-sharing scheme between stability, which reduces the risk to all parties, and making changes to reflect new scientific evidence. (This is a general issue for "commissioning by evaluation" for longer-term conditions, which we hope to pick up in dialogue with interested parties in reviewing the lessons from the RSS.)

→ AG response: We have noted this.

Section 13.1.11, first para (p 212) " Additionally, the assessment group believes that a review of the literature could have been undertaken to obtain more recent information [on the cost of a relapse]": same comment applies.

→ AG response: We have noted this.

Section 13.1.12 "health state utility values" (p 212): there is perhaps some slight confusion here. The "Boggild data set" was derived from RSS data (not from the original work by ScHARR) but, on advice from our Scientific Advisory Group, it was decided not to use it for the primary analysis of the year 6 and subsequent data. For our base run, therefore, we used the pooled data from the MS Trust and Heron datasets (the "2 pooled datasets"). The model provided to NICE also includes the facility to carry out sensitivity analyses using the Boggild dataset, either on its own or combined with the other two datasets (the "3 pooled datasets"). The sensitivity analyses we have carried out suggest that the choice between the "2 pooled" and "3 pooled" datasets is not critical.

→ AG response: We have noted this.

Section 13.1.14 "treatment effect" (p 212): there are several misunderstandings in this para. Firstly, we did not derive estimates of the relative rate of relapse from RSS data – the assumptions were taken from the 2001 ScHARR model, based on the then available RCT data. Secondly, the transition matrices for the "on treatment" cohort were not derived independently, but are obtained from the BCMS transition matrices by applying a hazard ratio for disease progression to all forward transitions (and assuming no effect on backward transitions). The hazard ratio is then varied by trial and error to obtain the same change in mean utility between baseline and year 10 as that actually observed in the RSS cohort. We call this the "implied hazard ratio" – for the DMTs in aggregate, this is the 0.7913 cited in this section. Thirdly, we do <u>not</u> assume that the hazard ratio for disease progression remains constant over the 50 year projection – in our base case we assume that the relative reduction reduces to 50% after year 10 (so the hazard rate to be applied from year 11 onwards is 1 – 0.5(1 – 0.7913) = 0.8957).*

→ AG response: We have undertaken a sensitivity analysis on our base case (base run model) where the time horizon is reduced to 20 years. We also undertook analyses using the time-varying model, which assumes that the relative rate of reduction reduces to 50% after Y10, and this model was run for a 50-year time horizon. This has been submitted to NICE as an Addendum (3).

Section 13.1.15 "relapse frequency" (pp 213-214): the estimates of relapse frequency by EDSS state come from the 2001 ScHARR model. Estimates of the treatment effect of the individual DMTs (the relative rate of relapse) also come from the ScHARR model, based on data from the RCTs. These estimates are generally very close to those derived by the Assessment Group as reported in chapter 15.

→ AG response: We have noted this.

Section 13.1.16 "treatment discontinuation" (p 214) "In the treatment arm of the economic model it was assumed that 5% of people discontinue treatment every year as a result of adverse events": the 5% is based on an analysis of the 8-year follow up data from the RSS. This is simply what we observed – no assumption is made about the reason for discontinuation of treatment. The analysis showed no obvious trend with time from baseline and only small differences between the individual DMTs.

→ AG response: We have noted this.

"Additionally, it appears that people who discontinued treatment continued to accrue treatment benefits without additional costs": this is a misunderstanding. Within individual cycles, as a result of the "half-cycle correction" applied in this (as in standard Markov models), the effect is that patients received a further year of treatment benefit in the year in which they discontinue treatment, but only on average half a year of costs. In following cycles, both the costs and benefits of treatment cease and patients who have discontinued treatment follow the same trajectory as patients who have never been treated. Sensitivity analysis showed that the minor inconsistency in relation to the in-cycle effects has only a very small impact on the average ICER.

→ AG response: We have noted this.

Section 13.1.18 "Time varying model" (p 215): it is perhaps worth emphasising that this "time varying model" (which uses different transition matrices for the first year after baseline and for subsequent years, in both the untreated and treated arms of the analysis) is different from the use of a time-varying treatment

effect, ie the assumption referred to above that the treatment effect reduces to 50% of its value after year 10. Calculations with the time varying model gave a rather more favourable ICER than those of the base case.

Section 13.2 "Summary of critical appraisal of the RSS model" (p 215): see comments above on the 5% discontinuation assumption and the 72% relative relapse rate. In addition

"The assessment group noted that there was an increased risk of mortality for people with MS when compared to the general population, as well as transition probabilities to EDSS 10 (MS-related death). Using this assumption would lead to double-counting MS-related deaths in the model": not necessarily. Our understanding is that there is evidence that people with MS are at higher risk of death from non-MS causes in addition to a risk of death from MS-related causes. This is what we have attempted to model. However, our sensitivity analyses showed that this is not a critical assumptions – changing the SMR for general mortality from 2 to 1 reduces the ICER (on our base case estimates) from £33,700 to £33,000.

→ AG response: We have noted this.

Section 14.1.19 (p 228) "In the [Biogen]model, people who progressed to a SPMS health state discontinued treatment": in the RSS cohort, the majority of patients who were assessed as switching to an SPMS state remained on their original DMT, at least for a period, even if the particular DMT was not licensed for use in SPMS. The clinical advisors to the RSS commented that the judgement on whether a patient had progressed to SPMS was quite subjective, and that clinicians often advised their patients to continue with active treatment until it was clear that they could obtain no further benefit. These considerations lay behind the advice of the RSS Scientific Advisory Group to drop the distinction between RRMS and SPMS in modelling disease progression for MS.

→ AG response: We have noted this.

Table 60, first row "natural history cohort" (p 248): it's slightly misleading to say that the Teva natural history model is based on the London Ontario cohort – the probabilities for transitions between EDSS states are derived from the BCMS dataset and it is only the probabilities for transition between RRMS and SPMS states that come from London Ontario (via the 2001 ScHARR model).

→ AG response: We have noted this.

Section 14.4.6, "Population studied" (p 254): "The assessment group consider that the age, sex and EDSS scores amongst those in the RSS dataset better reflect the UK RRMS population than participants recruited into a clinical trial": in general we agree, but there is some evidence that the patients recruited in the early years of the RSS may have contained a higher proportion of patients with long duration of disease at baseline (and therefore less potential to benefit from treatment) than a typical "incident" population. This would slightly bias the ICER against the DMTs. We provided evidence in this in the data supplied to NICE.

→ AG response: We have noted this.

Section 14.4.7, first para (p 255) "Teva used the London Ontario data84 to derive the majority of their transition probabilities to model progression": see above.

"Transition probabilities: treatment effect", second para (p 255) "The relapse rates on DMTs obtained from the network meta-analysis tended to be lower that that obtained from the 10-year RSS datasets": we weren't quite sure whether this referred to the relapse rates for untreated patients or the relative relapse rates for treated patients. Either way, we are not aware of any use of the RSS dataset for this purpose. We suspect that the reference should be to the assumptions from the 2001 ScHARR model which we took over without change for the base case RSS model.

Third para (p 256) "A higher discontinuation rate will lead to lower lifetime costs but also lower quality adjusted years on DMTs. This may potentially impact on the ICER estimate": our sensitivity analyses show that a higher discontinuation rate results in a more favourable ICER, probably because the greatest benefits from treatment (in the model) are those accrued soon after baseline. Using a discontinuation rate of 2.9% (the Assessment Group's estimate based on RCT data) rather than our estimate of 5% (from 8-year RSS data) increases the ICER from £33,700 to £38,500.

Fourth para (p 256) "Not including a waning effect will not impact on lifetime costs on DMTs but will increase quality-adjusted years on DMTs, and likely result in lower ICER estimates." there is an indirect effect on lifetime costs – assuming no waning results in slower progress to EDSS 7 (or to SPMS for models which make the distinction) and thus delays the point at which patients come off treatment. However, this increase in lifetime costs is greatly outweighed by the increase in QALYs so there is indeed a reduction in the ICER. On a 50-year horizon with our base case assumptions the ICER with "waning" is £33,700 compared to £25,300 without waning.

→ AG response: We have noted this.

Section14.4.8, 3rd para (p 257) "The costs assigned to the EDSS states in Biogen's company submission tended to be lower than that used by Teva and Merck. This is likely to result in lower lifetime costs, but will affect both DMT and BSC strategies": yes, but there is a bigger effect on the BSC strategy because untreated patients reach these higher EDSS states sooner. Other things being equal, using the resource costs in the Biogen submission will result in a less favourable ICER than those using the RSS base case estimates.

→ AG response: We have noted this.

Section 14.4.9, first para (p 257): the rather flatter curve of utility vs EDSS used by Biogen will result in a less favourable ICER.

→ AG response: We have noted this.

Section 14.5.1 (p 261) "Teva used the London Ontario dataset in order to model disease progression": see comments above – Teva in fact used BCMS data as their main source of information on disease progression. Because of the redacted information we cannot comment at this stage on the differences between the Teva estimates and those of other companies, but see below for a query about the hazard ratio (apparently) supplied by Teva.

→ AG response: We have noted this.

Section 5.1.4, para following table 64 (p 263): "Our combined annual probability of 2.29% is lower than the discontinuation rate assumed in the RSS model": we argue that the estimate derived from 8-year RSS data, representing normal clinical practice in the UK, is likely to be more robust than an estimate derived from short-term RCT data. If anything, our 5% estimate is likely to be an underestimate because we were not able to take account of patients discontinuing treatment after a switch to a non-scheme DMT (and also because we have evidence that patients who are lost to follow-up are more likely to have discontinued treatment than those who continue to be followed up).

→ AG response: We have noted this.

"Discontinuation rates reported by each company, tended to be lower than those derived from our clinical review": table 64 appears to show the opposite.

→ AG response: We have noted this. We will amend in the final pre-publication version.

Table 65 (p 264): The value of 0.6494 derived by the Assessment Group seems low compared with the spread of values for individual products given in the final column of the table – only Plegridy has a lower value (0.64) and the values for the other products are in the range 0.66 (Copaxone) to 0.80 (Avonex). I would expect an appropriately weighted average over the 5 products to be nearer 0.70, ie closer to the RSS value (which of course does not include a contribution from Plegridy).

Section "Treatment effectiveness: time to disability progression" (p 264) "The HR [from the Assessment Group's meta-analysis] was 0.6955 (95% CI [0.5530, 0.8747]). In contrast, the RSS model reported a reduced risk of sustained disease progression of HR 0.7913 (0.7705, 0.8122)": these two estimates are not comparable, for the reasons outlined in our covering note. In particular, it is not valid to take the hazard ratio of 0.6955, representing an estimate of the relative <u>net</u> rate of forward progression, and use it in a Markov model in which the hazard ratio is applied only to forward progressions and backward progressions are assumed to be unchanged.

→ AG response: We have noted this.

Section "mortality" (p 265) "In the RSS model we noted that individuals were subject to MS-related mortality (modelled as twice the standardised mortality rate from other causes)..": see above – it is <u>non</u>-MS (general) mortality which is modelled as twice the rate as for the general population.

→ AG response: We have noted this.

Section "resource use and costs" (p 266) "The costs of disease modifying treatments were obtained from the British National Formulary 2016": see covering note – this use of NHS list prices (instead of the "RSS prices" which will continue to be available to the NHS) will seriously affect the comparison between the 4 DMTs.

→ AG response: We have noted this.

Section "Utility values, including disutilities" (p 266): it appears that carers included in the analysis represent informal/unpaid carers. The NICE reference case suggests that the perspective should be all direct health effects, whether for patients or other people. Hence, the assessment group has excluded carers' disutilities from the main analysis": see covering note. We do not see the Assessment Group's logic – surely the disutility to a carer is a legitimate "direct health effect [on] other people"?

→ AG response: Please note our previous comments regarding carers' disutilities. We presented analyses with carers' disutilities in Appendix 9 of our original report (7). Moreover, an expanded set of analyses including carers' disutilities has been provided to NICE in Addendum 2 (with confidential and non-confidential analyses) (2, 3).

Section 15.1.5 (p 266) "We consider the RSS model base case with changes made to avoid double counting of mortality and removal of carer disutilities to be our base case": this statement slightly begs the question of what is the "RSS model base case". As noted above, we supplied NICE with two versions of the RSS model, one with a 50-year horizon and an explicit "waning" assumption (our preferred model, and the one agreed between the parties to the scheme) and one with no waning but a 20-year horizon. The Assessment Group's choice of a model with a 50-year horizon but no waning represents a further, very significant, change from the model supplied on behalf of the parties to the scheme and this should be explicitly recognised.

→AG response: We have noted this. In this context '*our* base case' refers to the Assessment Group's base case.

Table 60, "[relapse] rate ratio" (p 269): the confidence limits around the central value of 0.72 for the "RSS model" look very skewed (0.5262, 0.7623) compared to the more or less symmetrical confidence limits around the alternative estimate of 0.6494 for the Assessment Group model (0.5572, 0.7567).

→ AG response: In the absence of confidence intervals in the data provided to us from the DH and the RSS around this estimate, we used confidence intervals from our own detailed systematic reviews of randomised data and network meta-analysis in order to run the model probabilistically. In the addendum provided to NICE, we re-ran the probabilistic sensitivity analyses using the confidence intervals recently provided by the DH (1).

"Management costs" (p 269) and "Utilities" (p 270): it appears that, in the probabilisitic sensitivity analysis, the costs and utilities associated with each EDSS level are allowed to vary independently according to the specified distribution. This could have the paradoxical effect that, in some simulations, a patient moving to a higher EDSS level would incur <u>lower</u> costs and/or enjoy a higher utility as a result of the change in EDSS. Treatment, by slowing down the movement of patients to higher EDSS, would thus result in higher costs (in addition to the direct costs of treatment) and/or lower QALY gains. This appears to be the only plausible explanation for the otherwise incomprehensible finding that some replications have a negative QALY gain, ie appear in the "North west" quadrant of the cost vs QALY plot. I appreciate that this assumption of independent variation of each parameter is common in probabilitistic sensitivity analyses, but I would suggest caution so as not to over-interpret the results. An alternative approach is described in Appendix 2.

→ AG response: We have re-run the probabilistic sensitivity analysis using the confidence intervals included in Appendix 2 of this document (1, 3). We assumed independent variation of each parameter. The results of the simulations show that none of the replications are in the northwest quadrant.

On a separate point, we were not quite clear how the AG applied the parameters derived from the ScHARR model in calculating the variation of the EDSS-specific utilities about the mean value from the pooled MS Trust/Heron datasets. In the ScHARR model, the distribution of each utility is described by a 3-parameter beta distribution, in which the "a" and "b" parameters have their usual function (defining the "tightness" and degree of skew of a distribution defined in the interval [0,1]) and the "c" parameter has the effect of stretching out the distribution into the interval [c,1]. c is given the value -0.594, representing presumably the worst possible state of health. The mean of the distribution is determined by a combination of all 3 parameters. Using the values in the ScHARR model the means approximate to the values used in ScHARR's deterministic analysis, but the variation about the mean is very wide – eg for EDSS 0 the 95% confidence intervals are (0.12, 0.98) about a mean of 0.68, and for EDSS 9 the CIs are (-0.59,+0.48) about a mean of -0.36. This variation about the mean is far wider than that found in the MS Trust and Heron datasets, and almost certainly accounts for the very wide variation in cost per QALY (and the replications in the "north west" quadrant, ie negative QALY gain and positive incremental cost) found in the AG's analysis. We would strongly recommend repeating the analysis with a distribution derived from the pooled MS Trust and Heron data – see Appendix 2 for details.

→ AG response: Please see previous comment.

Tables 73-75 (pp 275-276): see covering note about the difficulty in making a fair comparison between Plegridy and the other products. Given this, it is unfortunate that the table presents the ICERs for the other products only versus Plegridy and not versus best supportive care. On a comparison against best supportive care, the ICERs for the individual products (excluding Plegridy) are in the range £14,000 to £26,000 for sensitivity analysis S2A, and £5,000 to £17,000 for analysis S2B.

[redacted]

→AG response: We have noted this.

Table 75 (p 276): we were puzzled at the figures given for Copaxone, which would imply an ICER versus best supportive care of [redacted]. *We do not know the exact assumptions used by the Assessment Group since these are redacted in Table 70. However, an ICER of this order of magnitude would require a relative hazard ratio for forward progression of around* [redacted] *which is much higher than the "implied hazard ratio" arising from the RSS year 10 analysis. The calculations in SA3 for both Avonex and Rebif appear to use the expected value of the implied hazard ratio. We therefore suggest that, for a fair comparison, Copaxone should be assessed on the same basis. This would result in an ICER of the order of* [redacted].

→ AG response: We have noted this.

Section "SA5: parameter uncertainty analysis" and Figures 26-27 (pp 278-279), "The model remained robust to changes to the treatment discontinuation rate and the model time horizon": this conclusion needs to be considered in relation to the size of the parameter variation adopted. For the discontinuation rate, a variation of ±10% means (presumably) a variation of between 2.7% and 3.1% about the AG's preferred value of 2.9%. This does not seem an adequate range given the difference between the AG's value, the value based on RSS data (5%) and the values submitted by the companies (up to 10.4% according to table 70). With a wider range of variation, this parameter makes a significant contribution to the overall uncertainty, though not as much as the other parameters considered by the AG. Similarly for the time horizon it is hardly surprising that a variation between 46 years and 54 years makes little difference, given that both costs and QALYs are discounted at 3.5%. On the contrary, adopting a time horizon of 20 or 30 years makes a considerable difference. (The AG present calculations for individual DMTs for these shorter horizons, but not for the DMTs in aggregate.)

Figure 29 (p 280): the acceptability curve seems very flat, and the finding that only 37% of the simulations achieved a cost per QALY of £20,000 or less must be some cause for concern (and slightly undermines the assertion in the abstract that the DMTs in aggregate are clearly cost effective). It is unfortunate that the AG did not examine more critically the assumptions which led to this finding. If it is driven by the assumptions on cost and utility as a function of EDSS (see above) then in my view figure 29 will greatly exaggerate the variation of the cost per QALY about the mean value given by the deterministic analysis.

→AG response: We have noted this.

Section 15.3.2 "Strengths and weaknesses", second para (p 283) "in particular, we did not have a confidence interval for the annualised relapse rate": a confidence interval was available in the 2001 ScHARR model from which this parameter was drawn. In any case, the sensitivity analysis reported in figures 26 and 27 shows that the ICER is not very sensitive to this particular parameter. We suggest that the lack of this particular confidence interval is hardly a major "weakness" of the analysis.

→ AG response: We have noted this.

2. Comments from NOVARTIS:

Page	***Text***	***Novartis questions***
60	*"We excluded:"* *"Studies that only examined patients with highly active or rapidly evolving MS, as best supportive care is not an appropriate comparator for these populations"*	*Novartis is concerned that the scope of this appraisal has not been clearly defined which may lead to misinterpretation of the guidance following publication.* *Even though all relevant interventions in the scope of this appraisal (interferon β-1a [Avonex® & Rebif®], interferon β-1b [Betarferon® & Extavia®], pegylated interferon β-1a [Plegridy®], and glatiramer acetate [Copaxone®]) could in theory be used to treat patients with highly active (HA) relapsing remitting multiple sclerosis (RRMS) and patients with rapidly evolving severe (RES) RRMS, it is clear from the exclusion criteria that the Assessment Group interprets the scope for this appraisal to exclude populations with HA RRMS and populations with RES RRMS, because best supportive care is not a relevant comparator in these populations and evidence from studies in these populations has been excluded.* *Therefore, please could NICE confirm that the assessment report conclusions only apply to first-line treatment of patients with active RRMS?* *Confusion around the scope is evident from:* *- the approach to the network meta-analysis conducted by Merck, including interventions/comparators outside the scope (fingolimod [Gilenya®] and natalizumab [Tysabri®] are licensed only in HA and/or RES RRMS) and* *- the approach to economic analysis conducted by Teva UK Ltd, including interventions/comparators outside the scope (fingolimod [Gilenya®] and natalizumab [Tysabri®] are licensed only in HA and/or RES RRMS).* *Novartis suggests that the Assessment Report clarifies that the scope excludes HA and RES RRMS and that analyses including treatments for these indications are therefore not relevant.*

→ AG response: This comment refers to the NICE scope. No clarification is required from the AG.

266	*"Disutilities associated with caring for people with multiple sclerosis were included in the RSS analyses. However, it appears that carers included in the analysis represent informal/unpaid carers. The NICE reference case suggests that the perspective should be all direct health effects, whether for patients or other people. Hence, the assessment group*	*Novartis is concerned that the Assessment Group has misinterpreted the reference case and that the approach towards in/exclusion of health effects and costs has been confused. It is stated in the NICE methods guide (2013) that: "For the reference case, the perspective on outcomes should be all direct health effects, whether for patients or other people. The perspective adopted on costs should be that of the NHS and personal and social services." (section 5.1.7).* *Please could NICE confirm that carers' disutilities (representing health effects, not costs) should therefore be included in the base case of the main analysis?*

	has excluded carers' disutilities from the main analysis."	

→ AG response: The results incorporating carers' disutilities were presented in Appendix 9 from page 436 of our original report (7). Moreover an expanded set of analyses including carers' disutilities has been provided in Addendum 2 (with confidential and non-confidential analyses) (2, 3).

Section 15 & 16	*Table 64, 65, 66, 67, 73, and 80 and in text on page 266, 275, and 285*	*Extavia® appears to be missing from several (but not all) tables and phrases throughout these sections when mentioning Betaferon®. Since they have been considered the same drug in the Assessment Report (page 38, section 5.3.1), could Extavia® please be added to the tables and text when Betaferon® is mentioned?*

→ AG response: We will amend in the final version.

3. Comments from ABN

Introductory comments

1. *This represents an ambitious and extensive piece of work by the assessment group. The methods and conclusions are transparent, well presented and comprehensible. The strategies for identifying relevant studies are well-defined. The agreed protocols appear to have been followed as intended. The review is clear, without apparent bias and credible.*

2. → AG response: We thank the ABN for their general comments on the AG report.
   With the exception of Plegridy, these drugs have been used extensively in the NHS, especially since the set up of the RSS in 2002. As neurologists, we approach this review with broad and long personal experience of using the medications, offering a different perspective than might be more usual in a NICE assessment of an emerging technology.
   The advent of newer therapies has led to marked changes in the way these drugs are used. In many centres, it is now unusual for naïve patients to choose an injectable therapy first line. Even before the advent of escalation therapies (natalizumab and fingolimod initially), switching between these drugs for reasons of tolerance and efficacy was common. The advent of newer therapies has meant that the models proposed here, whereby a patient is expected to stay on any one therapy long term, lack face validity.

   The history to this is, however, well known, and the 2002 decision that the drugs were not cost effective in the then-favoured model, has needed to be revisited for some time. The end of the RSS offers this opportunity, however, this exercise must be seen as very artificial and divorced from current practice, albeit an essential prerequisite to the subsequent evaluation of the newer therapies and evolving treatment strategies.

3. *It is important to treating physicians that the assessment's findings, albeit they are largely in favour of the drugs, are credible and robust to criticism, and potential areas of weakness are highlighted.*
4. *The prescribing community would value as wide a range of choices at each stage of the disease as is possible, allowing prescribing of drugs within the available clinical evidence and permitting patients a choice of initial therapy based on their needs and values, along with the chance to switch as dictated by tolerance or efficacy. Any proposed restriction placed on physician or patient choice by cost considerations, coming at this late stage in established practice, would require careful justification.*

5. *The assessment highlights the sometimes large and unpredictable effects of challenging underlying assumptions in the models. One of the main concerns with this appraisal is the potential impact of the outcome on the assessment of newer therapies. A good "sense check" on the final model would have been to see how some of the newer drugs, which are clearly superior to this group in terms of efficacy in day to day practice, would perform. It is an oddity of the way things have been done that we need to wait to look at a drug such as natalizumab which would have acted as a useful internal control of the power of these methods to detect a true difference. There is a risk that this assessment might need critically revisited if blatant inconsistencies emerge from later assessments based on these methods.*
6. *Any advice offered on future studies must be realistic for this appraisal's conclusions to maintain credibility. It is unlikely we will see any of these drugs used even in the control arm of a future DMT trial, so to propose a head to head or placebo controlled trial is pointless. At best, one might express regret that the chance to do such as study has been missed.*

→ AG response:. The ABN pointed out that switching between injectable first-line drugs is common. This is something of which we were aware. Unfortunately, we were not able to examine switching within the dataset we used to perform analysis.

Major points:

1. *The reasons for the focus on ARR, TTP3 and TTP6 as outcome measures in the NMA are clear, but the authors do little to justify how these equate to long term outcomes, or the justification for assuming any effect, let alone a sustained effect beyond the 2-3 years of the trial data. As key to the process, this should be discussed.*

→ AG response: We agree that a sustained effect of DMTs on ARR and TTP over the long term is a strong assumption. This is why we used this assumption only in sensitivity analyses. In the AG base case, we took into account TTP and ARR as observed in the long-term data available within the RSS.

2. *the term TTP is ambiguous:*
    a. *An important recent publication (Lublin et al Neurology 2014; 83:278) creates an important difference between worsening of the EDSS (which can be relapse driven, reversible, or driven by neurodegenerative mechanisms) and progression which should be reserved for irreversible deterioration of the EDSS on a presumed neurodegenerative basis. The use of the term progression in reference to short term outcomes unduly suggests a neuroprotective role for the drugs, or implied effect in delaying the onset of SPMS. It would be best if this distinction were made throughout the document in line with modern usage.*
    b. *This is particularly important when knowingly choosing TTP3 over TTP6 in the full knowledge that many of these worsenings are reversible and will not contribute to long term disability*
    c. *The wording itself is misleading. MS trials often have, for example, "time to EDSS 6" as an outcome measure. An effective therapy will delay time to EDSS 6, and this will be expressed as a time. This seems quite distinct to the use here:*
    "For example, a hazard ratio of 0.75 in group 1 as compared to group 2 means that at a point in the future, people without progression group 1 will have a 25% less chance of having disability progression as compared to people without progression in group 2."
    This refers to the risk of having progressed at a fixed (though variable between studies) time point. The HR does not reflect the delay to any disability milestone or fixed progression, and I find the term confusing in this regard

    d. *Assuming the method is understood correctly, this may unduly favour drugs with a short study (eg Plegridy) vs those with a long study (eg Betferon), if there is a genuine waning effect, as seen in the RSS, where there was a particularly marked year 1 effect, partially cancelled out*

by subsequent years. If only using "the point of data maturity" this may lead to erroneous conclusions.

e. *On a similar note, "Time to clinically definite MS" is used in the CIS analysis. Similar to the point on TTP3, this is misleading at first read. Again, you appear to mean "chance of having CDMS at a specific time point", not delay as expressed by time to eg median survival against the measure.*

→ AG response: We used disability progression as reported in most of the clinical trials and generally defined as an increase of EDSS score of at least 1.0 point for patients with a baseline score of 1.0 or more, or an increase of at least 1.5 points for patients with a baseline score of 0, confirmed after 12 weeks (TTP3) or after 24 weeks (TTP6). Please also note that we inserted a statistical glossary on page 30 of the original report (7).

3. *It is unclear what triggers inclusion of particular findings in the abstract*
   a. *The ARR result for GA in the NMA is included but the TTP3 results for R44 is not. Given that neither metric is shown as superior for ranking drugs in terms of long term efficacy, it may be a worry that, especially on casual reading, superiority of GA in other domains might wrongly be assumed*

→ AG response: This comment has been noted.

   b. *Plegridy is also given prominence in the summary, despite results being derived from a short trial. These results should be treated with more caution*

→ AG response: This comment is noted and we acknowledged this as a limitation in our original report (7).

4. *The CIS analysis is immediately out of date following the McDonald 2010 revisions (McD10). The term CIS has essentially been redefined between the time the studies were initiated and this analysis. It is not clear enough that this is a study of first demyelinating events representing a mix of early MS and true CIS. There must be no room for these conclusions to be applied uncritically to a "pure" CIS group. It is a shame that patient level data could not have been accessed to allow for a true appraisal of the CIS data and also, from the early MS subgroup, to inform models on early treatment of MS proper.*
5. *Especially given the uncertainty here, giving a clear steer on the superiority of one product in terms of cost effectiveness for CIS seems unsafe.*

→ AG response: We acknowledge these comments and would have wished to obtain data for these early MS subgroups, but this was unavailable.

6. *There is no recognition of different epochs of studies. This is a major, and well known, area of controversy in RRMS. There is nearly 20 years between the start of the Betaferon study and the Plegridy study. The patients forming the placebo arms are very different, and this has been extensively commented upon. At the simplest level, the ARR in the placebo groups differ greatly with trial epoch. Especially in the NMA, it appears the PBO groups are seen a constant, but it is not clear to what extent there is baseline matching or adjustment, and even with good methods, we know that people going into a PBO controlled trial in 2010 are a very self-selected group compared to 1988. This makes any attempt at network analysis at best risky, and there is little reassurance in the text that the technique is*

valid in this setting. While the results are, overall, not controversial, the apparent prominence given to Plegridy would seem to demand more qualification.

→ AG response: This has been noted.

7. *Section 13.1.12 – was the RSS subgroup used? It should be noted that the RSS used a subgroup of BCMS, selecting 898 patients eligible for DMTs under strict 2002 ABN guidelines. The average age was 37 and disease duration 8 years. This is quite different to current practice, and, importantly, it is not clear how valid it is to use these transition probabilities for a model starting at age 30, with, presumably, a mean disease duration of 3 years. Were fresh TPs derived for this cohort, perhaps bypassing the need for 2 relapses in the previous 2 years? It is not clear if this is the case.*

→ AG response: We used transition probabilities (TP)s as presented in the RSS model.

8. *For RRMS, we need more clarification on whether the RSS baseline (based on real patients on treatment compared to a synthetic cohort) or a completely synthetic model extrapolated from 2 year studies (as in SA1), is more valid. We would not want to complain about the more favourable outcome in SA1 and the choice it gives patients and physicians - and there exists a potential challenge from the PSA on the RSS model - but the RSS was established to address the very question of long term assumptions in cost effectiveness models. SA1 suggests tolerance for substantial price increases against a willingness to pay of even £20k which may not be justified.*

→ AG response: This is noted.

9. *The trial data reviewed here includes studies that are old, familiar and have been repeatedly re-analysed and presented. In line with their principles, the assessors have not included the wealth of real world data available on the comparative efficacy of these drugs and the changing ways in which they are employed. While the UK community is familiar with NICE's methods, the exclusion of potentially informative data, such as that available from MS BASE, on discontinuation rates, switching rates and comparative efficacy, should be explained, especially when it is replaced with assumptions and extrapolations from 2 year studies.*

→ AG response: In the face of a large project with time constraints, we chose to exclude observational designs other than the RSS (widely acknowledged to be lower in the evidence hierarchy) from our systematic review in order to concentrate on RCT evidence. In addition, we believe that our NMA is an entirely original and valid contribution to this area.

Minor points – in order through the document

1. *Section 4.1 TA32: insufficient evidence on long-term effectiveness; again 5.4. Short term effectiveness was accepted*
2. *peak incidence 40-45– this needs clarified. The MacKenzie paper based on GP records is an outlier from all others at 25-30 – in line with figures used later in this paper*
3. *section 5.1 – "2 or more genes" (>100 variants; rev Sawcer, Lancet 2014) – later section clarifies this, but reads oddly at this point*
4. *section 5.2: RES/ HA used incorrectly in 5.2. Terms defined by FDA/EMA only, not international consensus on their definition or significance*
5. *section 5.2: in line with Lublin et al Neurology 2014; 83:278 you should avoid the term "benign MS'*
6. *section 5.2: CIS will not develop into PPMS*

7. *R22 as well as R44 licensed for SPMS*
8. *section 5.4.2 – it is perhaps inviting unwanted comment to venture into these areas. EBV by Vienna consensus not isolated from B cells in MS despite early reports (Owens et al. MSJ 2012)*
9. *section 5.4.3 – imaging section not great – Gd not a "contrast" agent; oddly worded re chronic plaques and enhancement; no mention of MR measures of neurodegeneration which correlate better with longer term disability*
10. *CDMS – meaningful only in CIS trials, and now of uncertain significance – in most cases, no more than time to second relapse in a patient with MS. Probably best introduced as an obsolete term*
11. *section 5.6.1 – reword to make clear FSS are combined to form the DSS, or EDSS (later evolution of the original)*
    a. *avoid term wheelchair confinement – focus on retained ability*
    b. *avoid term benign MS*
    c. *risk factors – clarify phenotype*
12. *section 5.6.2 – effect of relapses on long term progression – effect of early vs late relapses probably worth a mention. Given this, should GA be given prominence on ARR data, and should abstract include a qualification on extrapolation of short term measures to long term efficacy*
13. *section 6.1: NAbs in practice – should reflect heterogeneity of practice – not universally tested in clinical practice but some centres do. Statement may reflect advisors practice, but testing is routine in many sites.*
14. *SmPC on Rebif – "relapsing MS" is used - not the same as RRMS*
15. *HA – for nat – again care in use of terms HA/ RES*
16. *Section 6.3 incorrect escalation criteria – see SMpC for fingo – does not require multiple relapses*
17. *Exclusion of proportion relapse free as an outcome measure is too dismissive. FDA have preferred this to prevent high relapsing individuals skewing figures. I think this demands more recognition as desirable, even though it is not available for many of the studies you review.*
18. *Steroid Rx and grading of severity is dependent on countries involved – some have mandatory hospitalization for steroids. It is hard to compare these between studies unless definitions have been standardised*
19. *CIS: discontinuation for all seems very low (face value vs PreCISE discontinuation of c13% in 2 years (Comi et al. Lancet 2009))*
20. *GA best but the cost effectiveness (albeit at a higher ICER) of Betaferon could be clearer*

→ AG response: Thank you, these minor points have been noted.

Comments from TEVA

Teva welcomes the Report published by the Assessment Group (AG) and is in agreement with the overall conclusions that Copaxone® and the other disease modifying therapies (DMTs) are cost effective treatments for multiple sclerosis (MS). We do, however, have some concerns regarding the appropriateness of some of the assumptions used by the AG in their modelling. In particular, it appears that a hazard ratio of around 83% is used for Copaxone® when costs per QALY were calculated using company estimates of effectiveness (Table 75). However, the "implied hazard ratio" for Copaxone® using the year-10 RSS data, as supplied in our submission (and confirmed by the Department of Health), is [redacted], with a similar value also derived from the network meta-analysis (NMA) conducted by Teva. Using these hazard ratios would result in an ICER of approximately [redacted] for Copaxone® as compared to [redacted] in the current Report. Please could the AG explain why they did not use the implied hazard ratio for Copaxone® from the RSS, particularly since it appears that they have used the equivalent ratios for the beta interferons, putting Copaxone® at significant disadvantage in terms of comparative cost effectiveness?

Another major issue related to the modelling is the prominence given to pegylated-interferon beta-1a (Plegridy), particularly in the summary sections of the Report, as the most cost effective treatment for relapsing-remitting MS (RRMS). It is also notable that these results differ greatly to those produced by Biogen Idec (the manufacturer of this product) who presented an ICER value of over £30,000, which is in line with the results for the other interferons. The results for pegylated interferon are based on one trial (ADVANCE)[ii] with several recognised and important limitations. The AG acknowledges these limitations, stating on p284 "…our assessment of Plegridy, in particular, relied on one trial with one year of follow-up…" and concluded that "…these limitations led us to believe, on balance, that the RSS was a better choice for the base case." Disability progression is the key input for the cost effectiveness modelling in MS, and this outcome was only measured as a secondary endpoint after only 48 weeks of therapy in ADVANCE.[ii] Guidance from the European Medicines Agency (EMA) in this area states that disability progression should be measured over at least 3 years.[iii] Another important caveat of the ADVANCE trial is that this was undertaken many years after the studies for Copaxone® and the other interferons, and represents a significantly different patient population. There is no evidence that pegylated interferon is any more efficacious than the other interferons or Copaxone®; undue emphasis should not be given to this single study, as was recognised in the AG's own main conclusions.

Whilst the Assessment Group acknowledges the limitations of the data available for pegylated interferon, it is disappointing that the main conclusion of the Report, in terms of cost effectiveness in RRMS, appears to place so much emphasis on a single, short-term study. It is also very surprising that the cost effectiveness results for Copaxone® and the (non-pegylated) interferons for RRMS (e.g. Table 73) are presented as an incremental analysis and therefore not versus best supportive care (BSC), but versus pegylated interferon. As per the scope, the effectiveness of the DMTs was firstly to be appraised versus BSC, and, if appropriate, versus each other. To those who do not examine the Report in detail, the way the results are presented gives the entirely misleading impression that most of the DMTs, except pegylated interferon, are being dominated by BSC. The results should be presented as per the scope.

Teva strongly recommends that the conclusions drawn in the Report fully reflect the evidence base as a whole and the limitations of the data available, with no undue prominence given to pegylated interferon on the basis of one study. The cost effectiveness results for Copaxone® should also be based on the implied hazard ratio from the RSS ([redacted]) to ensure a fair comparison versus the other DMTs. Overall, we feel that a fairer and more reasonable conclusion is that all the DMTs are cost effective for RRMS.

→ AG response: These comments have been noted. We have undertaken new analyses using the implied HR from the RSS (1).

Fact Checking of Assessment Group Report

Location	***Error/Issue***	***Correction***

p39	*Title of Section 5.3.2 is currently "Disease modifying therapies (glatiramer acetate)"*	*Copaxone® is only drug mentioned in section so change title to "glatiramer acetate" – consistency with section on beta interferons*

→ AG response: This minor point will be amended for the final version of the report.

p39 and p51	*"GA is indicated for the treatment of RRMS"* *"GA is indicated for the treatment of patients with RRMS"*	*Copaxone® is indicated for "relapsing forms of MS" (SmPC giving details on the populations in which clinical trials have been conducted: 20mg/ml has been studied in RRMS and CIS, 40mg/ml has been studied in RRMS)*

→ AG response: This comment has been noted. The licensed indications as it appears in the SmPC are reported on Table 2 of the original report (7).

p110	*Extension of Cop1 MSSG 1995 studied stated to be "up to 11 months"*	*Blinded extension was this long, but extension study is still ongoing*

→ AG response: This comment has been noted.

p110	*CONFIRM trial – not stated that Copaxone® was an unblinded reference arm (study used oral placebo)*	*Limitations of study are noted on p120*

→ AG response: This is noted.

p111	*Significance for time to relapse in GALA study not stated*	*"p<0.0001" to be added after "393 days vs 377 days"*

→ AG response: This is noted.

p128	*Copaxone® not included in written listing of NMA results: "Ranking of the drugs suggested…"*	*Add results for Copaxone®*

→ AG response: This is noted.

p164	*States that in Teva submission "Dosages were not specified… there is some ambiguity as to whether licensed doses or other dosing regimens included."*	*All available data (including unlicensed doses) were included in NMA to produce the most robust network possible. Results were presented as per the scope (licensed doses only)*

→ AG response: This is noted.

p164	*Report states that in Teva submission "It appears that both dosages of GA were pooled into one node in the analysis, but this was not clear."*	*Clearly stated up front in Teva's submission that Copaxone® was presented as a single entity as the dosing regimens are clinically equivalent*

→ AG response: This will be revised in the final version.

p230	*Teva's submission is not fully described*	*Teva provided the DoH approved RSS model with Copaxone® specific data and a de novo model to address aspects not covered by the RSS model. Teva requests that this is clarified in the Report*

→ AG response: This is noted.

p230	*Report states that "…fingolimod, nataliumab and dimethyl fumarate…" were included in cost-effectiveness analysis*	*These three treatments were only included for use as second-line therapy and this should be made clear in the Report (please note that natalizumab is also spelt incorrectly)*

→ AG response: This will be revised in the final version.

p230	*States that Teva model "…in the base case, based on the subset of patients in the RSS who received this DMT."*	*This does not reflect Teva's submission. The RSS model used RSS data and the de novo model used results from Teva NMA as their base cases. It is sometimes unclear in the Report which of Teva's models is being talked about*

→ AG response: This is noted.

p231	*"The probability of cost-effectiveness for glatiramer acetate (Ccopaxone) relative to best supportive care was…"*	*Correct to Copaxone®*

→ AG response: This will be revised in the final version.

Sections 14.2.3 - 14.2.22	*The model referred to is not clearly specified*	*Can the AG clarify whether theses sections describe the de novo model submitted by Teva?*

→ AG response: Appropriate referencing will be included in the final version.

p233	*Dose regimens in TEVA model stated as "300µg every other day" for IFN β-1b, "250µg every 2 weeks" for pegylated IFN β-1a and "500mg once daily" for fingolimod*	*These values were typographical errors within the model that did not affect the cost-effectiveness calculations. The correct values should be as per the SmPC for each product: 250µg every other day for IFN β-1b, 125µg every 2 weeks for*

		pegylated IFN β-1a and 0.5mg once daily for fingolimod

→ AG response: This will be revised in the final version.

P237	*The Report questions the relapse cost and mortality rate used within the Teva model*	*Both of these points were addressed by Teva through scenario analyses, but this is not mentioned in Report*

→ AG response: This will be added in the final version.

P238	*Disutilities from adverse events are stated to be taken from "…manufacturer submissions to NICE for … IFN β-1a 44µg SC three times weekly (Rebif)."*	*This information was taken from the SmPC for Rebif*

→ AG response: This will be revised in the final version.

P239	*Model assumptions stated to include "13. Patient access schemes for which data are publicly available are considered in the base case"*	*Teva model used current list prices in the base case*

→ AG response: This will be revised in the final version.

P248	*States that Teva used "Natural history cohort based on London Ontario natural history cohort"*	*This is correctly stated on p231: British Columbia dataset was used for RRMS transitions. London Ontario data was only used for RRMS to SPMS and SPMS transitions*

→ AG response: This will be revised in the final version.

P248/9	*Dose regimens in TEVA model stated as "300µg every other day" for IFN β-1b, "250µg every 2 weeks" for pegylated IFN β-1a and "500mg once daily" for fingolimod*	*These values were typographical errors within the model that did not affect the cost-effectiveness calculations. The correct values should be as per the SmPC for each product: 250µg every other day for IFN β-1b, 125µg every 2 weeks for pegylated IFN β-1a and 0.5mg once daily for fingolimod*

→ AG response: This will be revised in the final version.

p249	*States that Teva used hazard ratio "…derived from 10 year RSS" and "Sensitivity analysis based on manuf NWMA…"*	*The RSS model used RSS data and the de novo model used results from Teva NMA as their base cases.*

		Additional results from sensitivity analysis of NMA used for scenario analyses in de novo model

→ AG response: This will be revised in the final version.

P251	*States that "Relative risks of relapse were estimated from RSS data."*	*The RSS model used RSS data and the de novo model used results from Teva NMA as their base cases*

→ AG response: This will be revised in the final version.

p255	*"Teva used the London Ontario data to derive the majority of their transition probabilities to model progression..."*	*This is correctly stated on p231: British Columbia dataset was used for RRMS transitions. London Ontario data was only used for RRMS to SPMS and SPMS transitions*

→ AG response: This will be revised in the final version.

p261	*"Teva used the London Ontario dataset in order to model disease progression…"*	*This is correctly stated on p231: British Columbia dataset was used for RRMS transitions. London Ontario data was only used for RRMS to SPMS and SPMS transitions*

→ AG response: This will be revised in the final version.

p266	*"We derived annual costs of £7264 and £6681 (£6724) for treatment with IFN β-1b 250µg every other day (Betaferon) and glatiramer acetate (Copaxone®) 40mg SC three times weekly or 20mg SC daily, respectively."*	*Value should be £6704 as stated in Table 68*

→ AG response: This will be revised in the final version.

p272 and p273	*Hazard ratios from company submissions column states "Glatiramer acetate 20mg SC daily (Copaxone®)" and quotes redacted value from Teva's submission*	*This value was calculated for pooled Copaxone® data, as stated in Teva's submission*

→ AG response: This will be revised in the final version.

p276	*Table 75, 'company estimates of effectiveness': from back calculation it appears that a hazard ratio of ~83% was used to drive the ICER for Copaxone®*	*The correct hazard ratio for Copaxone®, as supplied by Teva, was the "implied hazard ratio" using the year-10 RSS data: [redacted] (this value has been confirmed by the DoH)*

→ AG response: We have revised the report accordingly (1).

p276	*Table 75 states results for "Glatiramer acetate 40mg SC three times weekly (Copaxone®)"*	*This was pooled Copaxone® data, as stated in Teva's submission*

→ AG response: This will be revised in the final version.

Whole Report	*Neutralising antibodies (NAbs) have been included within the scope of this appraisal but are only briefly mentioned in the Report and not considered during economic modelling*	*Teva's modelling indicates that NAbs have the potential to affect cost-effectiveness and so Teva requests the fact that they have not been included in the Assessment Group's model to be clearly stated in the Report*

→ AG response: Although NABs were included in the scope, the clinical impact of NABs is not clearly demonstrated. Monitoring of NABs is not part of routine practice in the UK.

4. Comments from MERCK

Cannot conclude that Pegylated IFN β-1a 125 µg is 'the most cost-effective option'.

Merck welcomes the main finding of the TAG report, the acceptance of disease modifying therapy as clinically and cost-effective in both RRMS and CIS. We accept that the placebo-controlled studies may reasonably be criticised for their short follow-up, but there is now an abundance of long-term studies on the efficacy of the interferons (interferon ß-1b, interferon ß-1a IM, and interferon ß1a SC) such as PRISMS[iv] *which provides evidence of long-term evidence for well over a decade.*

Merck recognises the difficulties in conducting network meta-analyses in MS, especially the likelihood and impact of heterogeneity. In part this may arise due to the period of time over which evidence has been generated in pivotal and other studies. In the case, of the longer acting interferon Pegylated IFN β-1a 125 µg (PLEGRIDY), the least is known from a placebo controlled study which was performed most recently. It consisted of a very different selected population (relapse rates in the placebo groups of studies into multiple sclerosis have been decreasing since the 1980s[v,vi] *and with study duration of just 48 weeks.*[vii,viii]

It is also generally recognised that the earlier in the disease RRMS patients are treated the better the outcome, and in the Pegylated IFN β-1a 125 µg trial patients began treatment at a lower EDSS stage than those incorporated in the original pivotal trials[ix] *(mean EDSS <2.5, mean duration of disease 6.5 years and less than 10% of patients previously treated.)*

There is evidence comparing the interferons with glatiramer acetate through head-to-head studies (BEYOND, REGARD and COMBIRx), but no such comparison is available involving pegylated IFN β-1a 125 µg that can inform the network, and this may be compounded by the factors noted above, (the short study duration and inclusion of patients with less active disease). The TAG report states, in summarising cost-effectiveness results, that Pegylated IFN β-1a 125 µg is the most cost-effective option. Despite the TAG's own misgivings regarding the evidence base for Plegridy, their conclusion is not qualified

"However, one limitation of the analyses undertaken with data from the NMAs is that they at times relied on sparse networks with uneven risk of bias throughout the network. For example, analyses relating to pegylated IFN β-1a 125 µg (Plegridy) relied on one trial that was not connected to any other trials except by a placebo comparator. Thus, any issues with the estimates derived from our review of clinical effectiveness would have been propagated through the analysis of cost effectiveness" (p302 TAG report)

This concern is compounded, given the changes in classification of MS between the time of PRISMS (PRISMS 1998 - RRMS by Poser criteria) and other placebo controlled trials of Interferon Betas and GA, and the single Pegylated IFN β-1a 125 µg study (ADVANCE 2014 - RRMS by 2005 McDonald criteria).

The final point here is that the hazard ratio (HR) for Rebif 44 versus pegylated IFN β-1a 125 µg (TTP3), is reported (p131) as 1.01 (95% confidence interval 0.59, 1.74). Yet despite this, and the other concerns noted above, the TAG's statement that Pegylated IFN β-1a 125 µg was the most the most cost-effective product is presented without any accompanying assessment of uncertainty. No explanation was provided as to why probabilistic sensitivity analysis (PSA) such as that performed for the pooled analysis is absent from the analyses of the individual products.

→ AG response: Using our deterministic results we concluded that pegylated IFN β-1a 125µg was the most cost-effective option, but we accept that there are wide confidence intervals around the relative effectiveness estimates of pegylated IFN β-1a 125µg versus other DMTs.

- **The use of Rebif's list price instead of the actual cost to the NHS**

In their assessment the TAG used Rebif's list price in its analysis of individual products. Whilst this is an acceptable approach when dealing with products that have 'Commercial in Confidence' prices, it should be pointed out clearly where there is a commercial in confidence agreement with the Department of Health (DH), equivalent to a Patient Access Scheme (PAS), in place for Rebif. The costs associated with Rebif in the TAG's analysis are therefore much greater than under this agreement (such that Rebif's ICER will be overestimated). In the case of Rebif the impact of this on the analyses (including comparison with pegylated IFN β-1a 125 µg) is compounded as the TAG notes (p266),, by their not having 'specifically' taken into account Rebif's marketing authorisation. Patients on Rebif 44 mcg three times per week may (and in many cases do) subsequently have their dosage reduced to 22 mcg three times per week and therefore have lower associated costs. This treatment pattern is not reflected in the TAG's model.

→ AG response: Additional analyses using price discounts and infrastructure contributions provided by each company have been performed and sent to NICE (2, 5).

- **Lack of clarity on which HRs were used**

In the TAG's Sensitivity Analysis 3 (SA3) (p267), the assessment group utilised efficacy data from the company submissions. Here the hazard ratios for confirmed disease progression and rate ratios for annualised relapse that were reported by each company were inputted to the model, as well as relevant discontinuation rates and list prices. It is difficult to understand whether the TAG utilised company NMA, or RSS results in this analysis. This is particularly important, as the validity of the analysis is reduced if RSS results were used for cross-comparison. Results from the RSS for individual products should not be compared with one another (due for example to likely selection bias within the scheme). Additionally, the RSS results for the DMT's should not be compared against estimates for pegylated IFN β-1a 125 µg based on randomised evidence (NMA).

→ AG response: We used NMA results from the company submission in this analysis.

- **Lack of clarity on the TAG's CIS model**

In the analysis for CIS, Rebif 44mcg is presented as having the lower HR for conversion to MS (0.48), and patients developing MS are treated according to the RRMS analysis (for each drug). In the TAG's RRMS analysis where each treatment is compared individually, Rebif generates a greater QALY outcome than any of the alternatives in the TAG CIS analysis. Given that patients who discontinue in the TAG's CIS model, who subsequently develop MS are then assigned outcomes based on the pooled RRMS analysis, it is unclear how the results in the CIS analysis come about. It would appear that discontinuation is an important driver in the TAG CIS model, particularly given the sensitivity analysis presented by the TAG.

→ AG response: This is noted.

Although the dosage applied for Rebif in CIS is 44mcg, the overall analysis relies on continued treatment following MS conversion. As in the RRMS analysis therefore, the use of list prices, and the failure to recognise the potential for some patients to be managed on 22mcg over the longer term will also impact the CIS analysis, particularly for Rebif.

→ AG response: This is noted and analyses have been undertaken and submitted to NICE, using an adjusted cost based on this new information (SA2, SA3 and SA4) (2, 3).

1.5. Exclusion of carer disutilities

In the main analyses, The TAG evidences the NICE reference case in recognising direct health effects, to the exclusion of any burden falling on informal carers. Caregiver burden in MS is clearly important, and has been incorporated in previous NICE appraisalsx as well as having been recognised by DH as an appropriate concern to be addressed in the RSS model. The reference case refers to direct health effects, whether for patients or other people. The exclusion of possible health effects on carers of people with MS represents a structural modification of the RSS model.

→ AG response: The results incorporating carers' disutilities were presented in Appendix 9 (page 436) of our original report (7). An expanded set of analyses including carers' disutilities was provided in Addendum 2 (with confidential and non-confidential analyses) (2, 3).

- **Adaptation of approach to mortality**

The TAG report notes the possibility of some duplication of mortality effects in the RSS model on which the Merck submission is based, as both a general standardised mortality ratio (SMR) and EDSS specific mortality rates are applied at higher EDSS levels; the former is an RSS assumption whilst the latter derives from the original Sheffield (ScHARR) model, and for which the separately estimated natural history progression probabilities are adjusted. In fact EDSS specific mortality is low at EDSS<8, and the impact on cost-effectiveness analyses of any duplication will principally relate to this as the common SMR applied to all patients is unaffected by treatment (though will modify overall mortality and therefore actual cost-effectiveness model results). In Merck's sensitivity analyses employing SMRs varied by EDSS, the ScHARR based EDSS specific mortality is set to zero.

→ AG response: This has been noted.

Conclusion

Merck agrees with the TAG's affirmation of the RSS analyses, which that found the relevant DMTs in this appraisal to be cost-effective. The TAG reported the MS society's comments that; "The range of treatment options allows for the differential way MS can affect individuals and their differential responses to DMTs." We support this principle and encourage approval for all the DMT's being assessed, so that for the patient and clinician, choice is maintained.

→ AG response: This is noted.

5. Comments from MS trust

We would like to make the following points about the Assessment Report:

- Overall, we are encouraged by the conclusion that these agents are cost-effective in both RRMS and CIS.
- We are particularly encouraged by the conclusion concerning CIS, given the mounting evidence that early initiation of disease modifying drug therapy after a first demyelinating event can delay or stop conversion to clinically definite RRMS.
- Overall, we are pleased to see that NICE has based the cost effectiveness analysis for RRMS on the RSS analytical model. It is gratifying that the investment of time and energy by 5,000 people with MS and the neurologists and MS nurses working with them to collect this data over ten years has resulted in such a major contribution to our understanding of the benefits of these therapies over a longer time horizon.
- We are, however, concerned about some changes to the RSS model which are not justified by the data. We are aware that the DH is making a detailed response in this context and we support the DH response.
- We are also concerned that NICE is not using the actual price the NHS is paying in its cost effectiveness assessment. In the data circulated NHS list prices have been used which overstate the cost significantly.
- We have some concerns regarding Plegridy, principally because of the lack of long term usage data. We urge NICE to treat the estimates on Plegridy with caution and not use them in a comparative manner with the other DMTs.

- We note that there is no inclusion of carer disutilities. It is our understanding that NICE included carer disutilites in other assessments, for example natilizumab. This inconsistency is not appropriate for a long term condition where severe disability is possible.
- The RSS data showed that discontinuation rates between the four drugs were very similar and a 5% discontinuation rate would be appropriate rather than calculating individual product assumptions from the original RCTs, which were over a short term.
- We welcome the research recommendations, particularly for further qualitative studies on the lived experiences of people with MS.
- We would welcome further research recommendations on a current definition of Best Standard Care, taking account of recent evidence and guidance about multidisciplinary MS care, and on the cost of relapse, taking account of social care and the wider personal and societal costs alongside healthcare costs.
- The wealth of real-world experience of these agents has certainly confirmed that at an individual patient level, different products will suit different individuals. Dosing schedules, storage, side-effects and tolerability will vary, so we stress that. having been shown to be clinically and cost-effective, **all these products should remain available as a treatment option for all eligible patients**.

→ AG response: As stated above, the results incorporating carers' disutilities were presented in Appendix 9 (page 436) of our original report (7). An expanded set of analyses including carers' disutilities was provided in Addendum 2 (with confidential and non-confidential analyses) (2, 3).

6. Comments provided to Healthcare Improvement Scotland by:

SUMMARY

Authors performed a systematic review of clinical and cost effectiveness of classical first line disease modifying therapies (DMTs) in relapsing remitting multiple sclerosis (RRMS), secondary progressive MS and clinically isolated syndrome (CIS). DMTs were compared against best supportive care and each other. Annualised relapse rate (ARR) and to progression at 3 months and 6 months were the main outcomes.

Authors evaluated 35 randomized clinical trials. The main findings is there was very little difference between the analyzed DMTs in reducing moderate or severe relapse rates in relapsing remitting MS, and all these drugs were beneficial against best supportive care. In their analysis, authors concluded that glatiramer acetate 20 mg sc had the "highest probability" of being the best in reducing annual relapses rates followed by Pegylated IFN B-1a. Interferon (IFN) B-1a had the "highest probability" of being the most effective. Pegylated IFN B-1a was the most cost effective DMT and glatiramer acetate was the most cost-effective treatment for CIS. However I believe that there are no significant differences regarding outcomes when comparing all first line treatments in RRMS.

The final conclusion is that beta interferons and glatiramer acetate are cost effective for the treatment of both, relapsing remitting MS and CIS. In ~~addition~~addition, the supportive evidence may be at high risk of bias; for this reason authors suggested comparative studies with longer follow up and systematic reviews and meta-synthesis of qualitative studies.

REPORT

This is a nice and well written, high quality, review. I believe that there is no outstanding omission of relevant data from literature.

→ AG response: We are grateful to Healthcare Improvement Scotland for their comments.

Authors performed a deep, evidence-based, review of the evidence available for the use of beta interferon and glatiramer acetate in RRMS and CIS. These DMTs have been used in the prevention of relapses in RRMS for almost 20 years and have been considered the first line treatment. There is a lot of information regarding tolerability, side effects and safety risk stratification in the literature. As most of patients are females, the concern with pregnancy is a fact that should be included in the analysis. We know that glatiramer acetate is the safest drug to be used in young females who want to become pregnant in the future. In addition its profile of better tolerability, as compared to beta interferons, makes this drug one of the drugs of choice as a first line in moderate active RRMS. We have also long-term data in the literature regarding the efficacy of IFN B-1a and IFN B-1b and glatiramer acetate for the prevention of relapses, and the level of efficacy of all these drugs seems to be similar. More data and analysis is required regarding Pegylated IFN B-1a.

I feel that the data about long-term efficacy regarding prevention of disability progression is indeed limited. Most of studies have focused on "time to progression at 3 and 6 months". This outcome seems to be insufficient when considering the progression of disability in the long-term in multiple sclerosis patients. In addition, many patients evaluated for progression at 3 or 6 months may be indeed under the effect of previous sequel disability caused by a recent relapse. There are no good quality studies that have evaluated the long term effect of glatiramer acetate or beta interferons on cognitive function and/or brain atrophy. So we have to recognize that the existing data about the use of DMT (beta interferons and glatiramer acetate) have focused on short-term outcomes (annualized relapse rate and short-term disability progression), and that the knowledge and data regarding the long-term effect for these drugs are limited.

Other methodological limitation of the analyses is the fact that populations are not comparable. Inclusion criteria used in the randomized clinical trials changed in the last 20 years, from Poser criteria, MacDonald criteria 2001, 2005 and 2010. In addition, it may be difficult to compare relapse frequency and natural history between contemporary patients diagnosed as having clinically definitive MS based on MacDonald 2010 criteria, a single first ever relapse plus contrast-enhancement plaques on MRI, from those who were recruited in the initial historical beta-interferon clinical trials based on "history of at least 2 relapses in the last 2-3 years". I wonder if British Columbia historical series used in the Risk Shared Scheme may have a more severe form of MS when compared with the diagnosis done recently in the last years with new onset or naive patients presenting with early MS diagnosis. This fact could have an influence to the cost-effectiveness data.

The field of multiple sclerosis is changing rapidly. We have now twelve different medications available including the new oral treatments used as a first line DMT (teriflunamide, dymethil fumarate), new formulations (glatiramer acetate 40 mg; possible generic medications), and other drugs used for highly active MS (natalizumab, fingolimod, alemtuzumab). In addition, it is expected that several new drugs (ocrelizumab, daclizumab, laquinimod, cladribine, among others) may appear in the market in the next few years. For this reason, there is an urgent need to establish treatment algorithms for RRMS.

In addition, we need comparative clinical studies to compare efficacy, safety, effectiveness between classical first line treatments (beta interferons, glatiramer acetate) and the new oral treatments (dymethyl fumarate and teriflunamide). Outcomes to be analyzed should include annualized relapse rate, long-term disability prevention, and cognition measures (clinical and radiological markers of brain atrophy).

There are other variables that need to be taken into account in the "real world", outside from evidence-based medicine, when considering the choice or election of a first line treatment for prevention of relapses in RRMS: patient's values and preferences, and a well informed balance between efficacy and safety (risk of serious adverse effects) should be taken into account. "Needle phobia" and "needle fatigue" are important issues when considering long-term adherence to injectables or oral first line treatments in MS. For this reason, a proper algorithm and also a formal review in the future of oral versus injectable first DMTs in RRS would be advisable.

Another point to be considered in the future is the possibility of switching to new formulations of glatiramer acetate. Authors found that glatiramer acetate was the most effective in reducing annualised relapse arte in RRMS. However many patients are willing to use 40 mg three times a week instead of daily formualtions; could have this an impact on this data and outcomes?; are there any available data regarding long-term prevention of relapses rates and disability progression with this new 40 mg glatiramer acetate formulation?

Authors evaluated the research priorities in this report. They recognized that one key flaw in the analysis of clinical effectiveness evidence is the lack of long-term follow-up studies, and this is another important point to be taken into account.

In summary, this is a good quality meta-analysis regarding beta interferons and glatiramer acetate in RRMS.

→ AG response: The comment on the use of drugs among pregnant women has been noted.

7. Comments from BIOGEN

Neutralising Antibodies

In section 5.3.1 (page 39) it is stated "given the biological nature of recombinant IFN-β, patients are at risk of developing neutralising antibodies (NABs) against IFN-β. NABs are thought to increase relapse rates and the rate of disease progression." This statement is not factually correct; there is no evidence to suggest NABs alter the underlying MS disease course. Rather, NABs are thought to reduce the effectiveness of DMTs which may subsequently increase relapse rates and disease progression (as correctly stated in section 6.1 [page 51]).

→ AG response: This is noted.

Carer disutilities

Carer disutilities were not included in base case analyses run by the AG. Given the chronic nature of the disease and the impact of the disease on individuals other than the patient due to care needs, Biogen believes it is appropriate to include carer disulitlites in the base case. Furthermore, the NICE reference case does not suggest that carer disutilities should be remove from base case analyses when inclusion of these may be appropriate. The NICE methods guide (Guide to the methods of technology appraisal https://www.nice.org.uk/process/pmg9/chapter/1-foreword) states (Section 5.1.7, page 34): "All direct health effects, whether for patients or, when relevant, carers". The NICE methods guide also states (Section 2.2.8, page 18): "As far as is possible, the scope identifies principal measures of health outcome(s) that will be relevant for the estimation of clinical effectiveness. That is, they measure health benefits and adverse effects that are important to patients and/ or their carers. The clinical outcome measures usually quantify an impact on survival or health-related quality of life that translates into quality-adjusted life years (QALYs) for the

evaluation of cost effectiveness". It should also be noted that all previous submissions have included caregiver disutilities and this has been accepted.

→ AG response: As stated above, results incorporating carers' disutilities were presented in Appendix 9 (page 436) of our original report (7). Further analyses including carers' disutilities have now also been provided to NICE. (2, 3).

Transition probabilities: disease progression, relapse and mortality

In Section 14.4.7 (page 256) it is stated: "Whilst it may be difficult to argue which of the London Ontario or British Columbia data sets provide the optimal representation of disease progression in MS patients not receiving DMTs, it would seem unorthodox to use patients recruited into the placebo arm of a clinical trial to represent this". For accuracy and context, Biogen requests that it be acknowledged that this has been standard practice in all recent Single Technology Appraisals (STAs) of DMTs, and that this has been accepted by respective ERGs. Furthermore, without use of placebo as an anchor point in the network meta analyses (NMAs) and moreover the assumption it is reflective of BSC (i.e. no treatment), comparative analyses would have been limited, especially for products falling outside of the UK Risk Sharing Scheme (RSS).

In Section 14.4.7 (page 257), it is also stated: "There were significant differences in how treatment waning effect was modelled in the three company submissions. Biogen assumed that there would be no treatment waning effect in their base case analysis, and assumed that the efficacy of DMTs would be maintained". For accuracy, Biogen requests that it is acknowledged that waning was considered in sensitivity analyses as part of the company's submission and this actually resulted in negligible impact on results.

→ AG response: This is noted.

Use of NHS list prices for DMTs

It is Biogen's understanding that some DMTs have discounts applied to list prices. [redacted] *In order to represent the true opportunity cost associated with these products and resultant cost-effectiveness, it would be appropriate to include these discounts when analyses are run.*

→ AG response: Additional analyses using price discounts and infrastructure contributions provided by each company have been performed and sent to NICE (2, 5).

Probabilistic sensitivity analyses (PSA)

In a number of PSA iterations, treatment is dominated by best supportive care and reports lower QALYs and higher costs. These scenarios are not clinically plausible or credible given active treatment has been proven to provide a direct clinical benefit to patients and thus higher overall QALYs compared to best supportive care. These results are likely driven by the large confidence intervals surrounding the utility values as taken from the 2001 ScHARR cost-effectiveness model. Due to the extremely wide confidence intervals applied to these utility values, which in Biogen's view are also clinically as well as statistically implausible the correlation between decreasing utility values and increasing MS severity is lost i.e. a higher utility (improvement in quality of life) will be applied to a more severe EDSS state than the EDSS state preceding it. This contrasts with what is observed in clinical practice and thus probabilistic results need to be placed in a context for appropriate interpretation and validity

→ AG response: Since the correct confidence intervals surrounding the utility values have now very recently been provided to us, we have been able to re-run the PSA and have submitted this to NICE (1).

References:

1. Melendez-Torres G, Auguste P, Armoiry X, Maheswaran H, Court R, Madan J, et al. Clinical and cost-effectiveness of beta interferon and glatiramer acetate for treating multiple sclerosis. ERRATUM to original MTA report submitted to NICE- October 2016.
2. Melendez-Torres G, Auguste P, Armoiry X, Maheswaran H, Court R, Madan J, et al. Clinical and cost-effectiveness of beta interferon and glatiramer acetate for treating multiple sclerosis. MTA report: Addendum 2 to original MTA report with CONFIDENTIAL analyses submitted to NICE- October 2016.
3. Melendez-Torres G, Auguste P, Armoiry X, Maheswaran H, Court R, Madan J, et al. Clinical and cost-effectiveness of beta interferon and glatiramer acetate for treating multiple sclerosis. MTA report: Addendum 2 to original MTA report with NON-CONFIDENTIAL analyses submitted to NICE- October 2016.
4. NICE. Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis, Technology appraisal guidance [TA127]. 2007.
5. Melendez-Torres G, Auguste P, Armoiry X, Maheswaran H, Court R, Madan J, et al. Clinical and cost-effectiveness of beta interferon and glatiramer acetate for treating multiple sclerosis. MTA report: Addendum 1 to original MTA report submitted to NICE- August 2016.
6. Palace J, Bregenzer T, Tremlett H, Oger J, Zhu F, Boggild M, et al. UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model. BMJ open. 2014;4(1):e004073.
7. Melendez-Torres G, Auguste P, Armoiry X, Maheswaran H, Court R, Madan J, et al. Clinical and cost-effectiveness of beta interferon and glatiramer acetate for treating multiple sclerosis. Original MTA report submitted to NICE- August 2016.

Executive Summary

- **Multiple sclerosis (MS) is a chronic, progressive, lifelong disease, which affects the central nervous system (CNS), resulting in irreversible disability and a substantial patient and economic burden (1, 2).**
- **There is no cure for MS but disease-modifying therapies (DMTs) can slow disease progression (3).**
- **This submission is concerned with interferons (IFNs) and glatiramer acetate (GA); the two Biogen Idec's products of relevance to this submission are therefore intramuscular (IM) IFNβ-1a 30 µg (Avonex®) and subcutaneous (SC) pegylated (peg) IFNβ-1a 125 µg (Plegridy®).**
- **Both IM IFNβ-1a 30 µg and SC pegIFNβ-1a 125 µg have demonstrated efficacy in clinical trials and both have favourable safety profiles.**
- **In an economic evaluation, SC pegIFNβ-1a 125 µg was more effective and less costly than all other current IFN and GA treatments and may therefore be considered the treatment of choice among the treatments included in this MTA in patients with relapsing-remitting multiple sclerosis (RRMS). However, all treatments included in this MTA provide valuable options as a range of DMTs is required in order to best meet the clinical and individual needs of each patient (4). IFNβ-1a 30 µg was found to be cost-effective in the UK Risk-Sharing Scheme (RSS).**
- **It is important to note that SC pegIFNβ-1a 125 µg was not part of the original RSS and was recognised by the CHMP as a New Active Substance (NAS). Other products not included in the RSS but considered in this MTA are SC IFNβ-1b 250 µg (Extavia®) and GA 40 mg (Copaxone®).**
- **Biogen Idec's base case analysis uses the British Columbia natural history dataset, which can be considered a conservative analysis and consistent with findings from the RSS. The original analysis in the RSS used the London Ontario natural history dataset, which has also been included as a scenario analysis.**

Background

Multiple sclerosis (MS) is a chronic, progressive, lifelong disease, which affects the central nervous system (CNS) and results in the accumulation of irreversible disability. Approximately 85% of the population with MS experience relapsing-remitting multiple sclerosis (RRMS) during their initial disease course (5), characterised by episodes of unpredictable neurological attacks (relapses) separated by periods of apparent stability (remission). Relapses result in disability from which there is full or partial recovery, although recovery becomes diminished with repeated relapses leading to sustained disability progression (6-8). Even during periods of remission, new or enlarging CNS lesions are frequently detected on magnetic resonance imaging (MRI) scans (4, 9), indicating ongoing inflammatory disease activity and resulting in further disability progression (10, 11). RRMS is typically preceded by clinically isolated syndrome (CIS), a first clinical episode with features suggestive of MS lasting ≥24 hours (12). If left untreated, the majority of patients with RRMS (50–60%) develop secondary-progressive multiple sclerosis

(SPMS), a period of steady progression of neurological damage with fewer or no relapses, within 15–20 years after disease onset (13).

The accumulation of physical and mental disability associated with MS has a devastating impact on patients, affecting their physical and cognitive functioning and quality of life (QoL) (14). In addition, MS is associated with a significant economic burden (1, 2), both in terms of direct medical costs and non-medical costs to the social care system and wider society. Costs substantially increase with increasing disability: at low levels of disability (Expanded Disability Status Scale [EDSS 0.0]), the direct costs of RRMS in the UK are approximately £937 per patient per year compared with approximately £27,472 at higher levels of disability EDSS 7.5–8.0 (15). When societal costs are included, the total cost per patient per year can be as high as £103,076 at EDSS 7.5–8.0 (all costs inflated to 2015 values) (15).

There is currently no cure for MS and current treatments aim to reduce disease activity to slow or prevent disability progression (3). There is substantial evidence demonstrating that initiation of a disease modifying therapy (DMT) early in the disease course leads to improved outcomes as compared with delayed treatment in patients with MS (3, 4). DMTs vary in terms of their effectiveness, tolerability, and methods and timings of administration. Current guidelines from the Association of British Neurologists (ABN) therefore state that, in order to meet the clinical and individual needs of each patient, it is essential that the full range of DMTs can be prescribed by neurologists (4). DMTs currently available in the UK include: alemtuzumab, dimethyl fumarate, fingolimod, glatiramer acetate (GA), interferons (IFNs), natalizumab, and teriflunomide, all of which have been shown to be effective in reducing relapse rates and MRI lesion accumulation in patients with RRMS (4). However, at the request of NICE, this submission is only concerned with IFNs and GA, which include:

- IM IFNβ-1a 30 µg once weekly (Avonex®)
- SC pegIFNβ-1a 125 µg every 2 weeks (Plegridy®)
- SC IFNβ-1b 250 µg every other day (Betaferon® and Extavia®)
- SC IFNβ-1a 22 or 44 µg three times weekly (Rebif®)
- SC GA 20 mg once daily or 40 mg three times weekly (Copaxone®).

The clinical evidence for the efficacy and safety of the two Biogen Idec products (IM IFNβ-1a 30 µg and SC pegIFNβ-1a 125 µg) is discussed in this submission. In addition, these products are compared with other DMTs of relevance to this MTA in terms of clinical and cost-effectiveness.

IM IFNβ-1a 30 µg (Avonex®)

IM IFNβ-1a 30 µg first received European marketing authorisation for the treatment of RRMS in 1997, with the indication extended to include patients with CIS in 2002 (16). There is therefore substantial experience of the use of IM IFNβ-1a 30 µg in both clinical trials and clinical practice. The efficacy and safety of IM IFNβ-1a 30 µg for the treatment of RRMS was established in a pivotal 2-year, double-blind, randomised, placebo-controlled trial (MSCRG (17)) and its open-label extension (ASSURANCE (18)), which provided data up to 15 years. Results of MSCRG and ASSURANCE demonstrated that, in patients with RRMS, IM IFNβ-1a 30 µg:

- Significantly reduced the proportion of patients with sustained EDSS disability progression over 6 months by 37%, compared with placebo, over 2 years (21.9% vs 34.9%, p=0.02) and reduced mean EDSS scores at 15 years compared with no treatment or another DMT (4.4 vs 5.7; p=0.011).

- Significantly reduced the annualised relapse rate (ARR) by 32% compared with placebo in patients who completed 2 years of follow-up (0.61 vs 0.90, p=0.002).
- Was well-tolerated, with no new safety concerns identified over 15 years of use.

The efficacy and safety of IM IFNβ-1a 30 µg for the prevention of clinically definite MS (CDMS) in patients with CIS was also demonstrated in a 3-year randomised, double-blind, placebo-controlled study (CHAMPS (19)) and its open-label 5 and 10-year extensions (CHAMPIONS and CHAMPIONS extension (20, 21)). Results of CHAMPS and CHAMPIONS demonstrated that, in patients with CIS, IM IFNβ-1a 30 µg:

- Significantly reduced the probability of CDMS development by 51% over 3 years, compared with placebo (adjusted rate ratio [RR] 0.49, 95% confidence interval [CI] 0.33–0.73; p<0.001).
- Significantly reduced the rate of CDMS at 10 years by 39% when initiated immediately after disease onset compared with when initiated after 3 years (adjusted hazard ratio [HR] 0.61, 95% CI [0.45-0.82]; p=0.001).

SC pegIFNβ-1a 125 µg (Plegridy®)

SC pegIFNβ-1a 125 µg is a new molecular entity containing IFNβ-1a that received European marketing authorisation for the treatment of RRMS in 2014 (22). Pegylation of IFNβ-1a allows its serum half-life to be prolonged, providing the least frequent dosing schedule of any self-injectable treatment (22), which may enhance treatment adherence since dosing frequency appears to be linked to adherence (23). The efficacy and safety of SC pegIFNβ-1a 125 µg has been demonstrated in a 2-year, pivotal, randomised, double-blind trial, which was placebo controlled in the first year, after which patients receiving placebo were re-randomised to receive one of two SC pegIFNβ-1a 125 µg dosing regimens (ADVANCE (24, 25))[1]. Longer-term efficacy and safety has also been demonstrated in ATTAIN (26-30), a 2-year extension of ADVANCE. Results of ADVANCE and ATTAIN demonstrated that, in patients with RRMS, SC pegIFNβ-1a 125 µg:

- Significantly reduced the ARR (35.6% reduction; 0.256 vs 0.397; p=0.0007) and the proportion of patients who relapsed (39.0% reduction; 0.187 vs 0.291; p=0.0003) compared with placebo at 1 year.
- Significantly reduced the risk of disability progression sustained for 3 months (38.0% reduction; 0.068 vs 0.105; 95% CI [0.40-0.97]; p=0.0383) and for 6 months (54.0%

[1] Based on mechanistic considerations, it was assumed that SC pegIFNβ-1a 125 µg is at least as effective as currently available IFNβs (or other self-injectables, e.g. GA) and a superiority study vs an active comparator was not deemed scientifically appropriate. A formal non-inferiority study vs an active comparator was considered, but, following scientific advice and regulatory guidance, this option was not adopted since the number of patients required was deemed to be too large to be feasible and realistic. A placebo-controlled design was therefore chosen following careful consideration of potential ethical concerns. Given the number of current treatment options for patients with RRMS, it was decided that a 1-year placebo controlled phase with a second year to demonstrate the longer-term safety and efficacy of pegIFN was most ethically appropriate.

reduction; 0.040 vs 0.084; 95% CI [0.26-0.81]; p=0.0069) compared with placebo at 1 year.

- Significantly reduced the mean number of new or newly enlarging T2 lesions by 67% (3.6 vs 10.9; 95% CI [0.27-0.40]; p<0.0001) compared with placebo at 1 year.
- The reductions in relapse frequency, disability progression and MRI lesion burden were maintained in the second year of ADVANCE in patients with continuous Plegridy treatment.
- Was well-tolerated over 4 year of treatment, with a safety profile that was consistent with the safety profiles of established IFNβs for MS.

Early initiation of SC pegIFNβ-1a 125 µg was also shown to be beneficial: all efficacy endpoints at 2 years significantly favoured patients who received SC pegIFNβ-1a 125 µg over both Years 1 and 2, compared with patients who received SC pegIFNβ-1a 125 µg after 1 year of placebo.

Comparative efficacy and safety

Mixed treatment comparisons (MTCs) demonstrated that all treatments assessed in this MTA, including IM IFNβ-1a 30 µg and SC pegIFNβ-1a 125 µg, were effective in reducing relapses and disability progression compared with placebo. The results of MTC analyses were used to provide values for treatment effects on disease progression for patients with RRMS in the economic model. It was not possible to include data for patients with CIS in MTCs as studies including these data were not sufficiently comparable.

Pharmacoeconomics

An economic model has been developed to assess the cost-effectiveness of IM IFNβ-1a 30 µg and SC pegIFNβ-1a 125 µg, compared with best supportive care (BSC) and the other available treatments for RRMS. In comparisons with BSC using the British Columbia MS dataset, SC pegIFNβ-1a 125 µg had the lowest incremental cost-effectiveness ratio (ICER) of any treatment (£31,044/ quality-adjusted life year [QALY]), while all other treatments had ICERs >£36,000 per QALY (the Risk-Sharing Scheme [RSS] threashold). However, it should be noted that BSC was only included in the model at the request of NICE; in reality, BSC is not a relevant comparator for the majority of patients and is therefore not representative of best practice clinical care (4).

SC pegIFNβ-1a 125 µg was also dominant (i.e. more effective and less costly) compared with all other current treatments (Table 1). As SC pegIFNβ-1a 125 µg is a new treatment and has only recently become an option for MS patients, comparison with active treatment is particularly relevant as a true comparison of the opportunity cost. The ICER for IM IFNβ-1a 30 µg vs BSC was £63,163/QALY and ICERs of other current treatments vs IM IFNβ-1a 30 µg are presented in Table 1.

Table 1: Summary of ICERs vs IM IFNβ-1a 30 µg and SC pegIFNβ-1a 125 µg

Treatment	ICER vs IM IFNβ-1a 30 µg	ICER vs SC pegIFNβ-1a 125 µg
BSC	LCLE	LCLE
IM IFNβ-1a 30 µg	-	Dominated
SC pegIFNβ-1a 125 µg	Dominating	-
SC IFNβ-1a 44 µg	Dominating	Dominated
GA 20 mg	LCLE	Dominated
GA 40 mg	LCLE	Dominated
SC IFNβ-1b 250 µg (Betaferon®)	Dominated	Dominated

Treatment	ICER vs IM IFNβ-1a 30 µg	ICER vs SC pegIFNβ-1a 125 µg
SC IFNβ-1b 250 µg (Extavia®)	Dominated	Dominated

Abbreviations: BSC, best supportive care; GA, glatiramer acetate; ICER, incremental cost-effectiveness ratio; IFN, interferon; IM, intramuscular; LCLE, less costly less effective; pegIFN, pegylated interferon; SC, subcutaneous.

The inclusion of societal costs (including direct non-medical and indirect costs) in scenario analysis further demonstrates the value of the treatments included in this MTA. All IFNβ treatments dominated BSC when societal costs were included in the analysis. The impact of societal costs is increasingly relevant from a payer perspective in the context of a general movement to greater integration of health and social care.

Conclusion

IM IFNβ-1a 30 µg and SC pegIFNβ-1a 125 µg are effective and well-tolerated treatments for RRMS. [redacted]. It is an important and trusted DMT in the physicians' armamentarium in treating RRMS. SC pegIFNβ-1a 125 µg builds on this heritage, and provides the lowest dosing frequency of any self-injectable treatment, which may support treatment adherence. SC pegIFNβ-1a 125 µg was shown to be the most cost-effective treatment option for RRMS in the economic evaluation and may therefore be considered the treatment of choice of the treatments included in this MTA. However, all treatments included in this MTA are valuable options which help to meet the clinical and individual needs of each patient, and are endorsed as relevant therapeutic options by the most recent guidelines issued by the ABN (4).

1. Executive Summary

- In patients with relapsing-remitting multiple sclerosis (RRMS) Rebif® has demonstrated short- and long-term efficacy in reducing relapses and delaying disease progression when compared with best supportive care (BSC).[1-4]
- In patients with clinically isolated syndrome (CIS), Rebif® studies have also demonstrated a reduction in the number of patients who progress to a diagnosis of MS over the short and long term when compared with BSC.[5,6,77]
- In trials including subsets of patients with secondary progressive MS with relapses (SPMS), Rebif® has been shown to significantly delay disease progression vs placebo.[7]
- Rebif® has a well-established safety profile with an estimated over 1.35 million patient-years of treatment exposure during clinical trials and real-world experience.[8]
- The large-scale UK Multiple Sclerosis Risk-sharing Scheme (RSS) in RRMS was established to assess whether disability progression was consistent with clinical studies. It aimed to evaluate the long-term effectiveness and cost-effectiveness of Rebif® along with three other disease-modifying treatments when compared with a natural history cohort.[9]The cost-effectiveness assessment would be determined by the achievement of a therapy-specific hazard ratio for disease progression.[9]
- Rebif® has successfully demonstrated achievement of this hazard ratio[10] and these data corroborate the hazard ratio demonstrated in the pivotal phase III PRISMS study in RRMS.[1]
- As a result, Rebif® is confirmed as a cost-effective therapy according to the criteria set by the Department of Health in the RSS and is therefore a cost-effective use of NHS resources when compared with best supportive care.
- Additional cost-effectiveness analyses are presented in this submission in which the cost-effectiveness of Rebif® for patients with CIS and SPMS with relapses has been demonstrated.

MS: a debilitating disease with onset in young adults

Multiple Sclerosis (MS) is the most common debilitating neurological disease among young adults.[11, 12] The annual incidence of MS in the UK is approximately 4 per 100,000, and about 100,000 people are living with MS.[13, 14] MS is three times more common in women than in men.[14]

MS is caused by immune-mediated destruction of myelin, the coating surrounding nerve fibres in the central nervous system. Gradual destruction of myelin means the affected nerves can no longer function properly, leading to a range of debilitating symptoms and often to progressive disability. Areas of myelin loss/scarring are known as lesions and are visible by MRI.

Relapsing-remitting MS (RRMS) accounts for about 85% of MS cases.[15] It is characterised by periods of symptomatic disease activity known as relapses, interspersed with periods of remission.

RRMS is burdensome for patients, caregivers and society

Common symptoms of MS include visual disturbance, limb weakness, fatigue, bladder or bowel impairment. Relapses are acute inflammatory demyelinating events in the CNS, and typically last for several weeks.[16] As the disease progresses, difficulties with speech, memory and mental functioning become common.[17] Before the introduction of disease-modifying treatments (DMTs) such as Rebif® (interferon beta 1-a, three times weekly, t.i.w), approximately half of people diagnosed with MS would require walking aids within 12 years of diagnosis, and within 20 years approximately half would need a wheelchair.[18-20] With Rebif® up to 86% of patients did not require a walking aid (as indicated by EDSS$\leq$6) after long-term treatment of up to 15 years.[2]

As the disease progresses its impact on sufferer's health-related quality of life (HRQoL) increases.[21,22] People with MS are reported to have an average utility (a way of measuring HRQoL on a 0 to 1 scale) of approximately 0.5.[23] The disability associated with MS also negatively affects the HRQoL of family members who act as caregivers.[24]

The financial burden of MS

The total annual cost of MS in the UK was estimated to be approximately £1866 million at 2008 prices.[25] These encompass health, social services, employment, benefits, transport, and housing.[26]

Symptoms of MS such as incontinence, spasticity, visual problems and mobility problems all require treatment and thus generate costs. The cost of DMTs is only a small part of the overall cost of managing MS.

- The costs of MS increase as people become more disabled.[23,27] Increasing progression of disability is the main driver of increasing costs, both direct (i.e. costs to the NHS) and indirect (i.e. costs to wider society such as disability benefits and lost productivity).
- A study of the range of costs associated with increasing EDSS score in 5 countries including the UK estimated that annual cost per patient at the lower range of disability (EDSS Score $\leq$3) was €13,534-22,461 compared with €39, 592-65,395 at EDSS Score >7.[26]
- Relapses are also associated with increased costs.[27]

Rebif® is an effective treatment for MS

Rebif® is indicated for the treatment of patients with relapsing multiple sclerosis. Additionally it is indicated in:[28]

- Patients with a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis.
- Patients with secondary progressive multiple sclerosis (SPMS) with ongoing relapse activity.

The dosage for patients who have experienced a first demyelinating event (CIS) is 44 micrograms (mcg) of Rebif® given three times per week (t.i.w) by subcutaneous injection.

For RRMS: after titration, the recommended dosage of Rebif is 44 mcg given three times per week by subcutaneous injection. A lower dose of 22 mcg, also given three times per week by subcutaneous injection, is recommended for patients who cannot tolerate the higher dose in view of the treating specialist.

Efficacy in the pivotal study in RRMS

In the pivotal study in RRMS, PRISMS,[1] Rebif® was investigated at 22 and 44 mcg t.i.w. against a placebo arm. After 2 years of follow-up:

- The mean number of relapses per patient was 1.73 for the Rebif® 44 mcg group and 2.56 for the placebo group, a risk reduction of 33% (95% confidence interval 21–44%) at 2 years. [1]
- The time to first relapse was prolonged by 3 and 5 months in the 22 mcg and 44 mcg groups respectively, and the proportion of patients relapse-free was significantly increased (twice as many in the Rebif® 44 mcg group compared with placebo, $p<0.05$). Rebif® delayed progression in disability and decreased accumulated disability during the study.
- The disease burden (as shown by T2 lesions on MRI) increased by a median of 10.9% from baseline with placebo, compared with a median decrease of 3.8% in the 44 mcg Rebif® group ($p<0.0001$).
- The number of T2 active lesions on the biannual scans was also significantly lower (difference 67% and 78%) in the 22 and 44mcg groups than in the placebo group ($p<0{\cdot}0001$).

The benefits of Rebif® in RRMS are maintained in long-term use (Risk-sharing Scheme and PRISMS follow-up)

Importantly, as a demonstration of real-world long-term evidence, the large-scale UK Multiple Sclerosis Risk-sharing Scheme (RSS) in RRMS was established to assess whether disability progression was consistent with clinical studies. It aimed to evaluate the long-term effectiveness and cost-effectiveness of Rebif® along with three other DMTs, and compared them with a natural history cohort from British Columbia (BC), Canada. A total of 4137 patients were included in the clinical cohort and the follow-up was for 10 years.

- The 6-year data published by Palace et al,[29] determined that the aggregate data from the four products in the RSS demonstrated a slower EDSS progression for treated patients than predicted for untreated controls. These findings from this large observational study of treatment with interferon-beta or glatiramer acetate provide evidence that their effects on disability in patients with relapsing-remitting multiple sclerosis are maintained over the 6 years.

- The study continued to the 10-year completion point; though the results have yet to be published, the year 10 analysis is available and the data for Rebif® is contained in this submission.

In addition, the follow-up of the pivotal PRISMS study has also demonstrated the benefits of Rebif® over the long term. The annual relapse rate at 4 years in PRISMS was 0.72 in patients originally randomised to Rebif® 44 mcg, compared with 1.02 in patients who crossed over from placebo to Rebif® at 2 years ($p < 0.001$).[4]

- Time to sustained disability progression was prolonged by 18 months in the original 44 mcg group compared with the crossover group ($p = 0.047$) at four years.[4]
- After 8 years, patients originally randomised to Rebif® 44 mcg showed lower EDSS progression, relapse rate and T2 burden of disease than those in the late treatment (crossover) group.[3]
- 291 patients in the original PRISMS cohort are included in the 15-year analysis.[2] Higher cumulative dose exposure and longer treatment time appeared to be associated with better outcomes on: annualised relapse rate, number of relapses, time to EDSS progression, change in EDSS, proportions of patients with EDSS ≥4 or ≥6, ≤5, relapses and EDSS <4 or <6, and time to conversion to secondary-progressive MS (SPMS). Higher dose exposure was associated with lower proportions of patients with EDSS progression and conversion to SPMS, and longer time on treatment with lower risk of first relapse.
- Only 2 in 10 patients on Rebif® converted to SPMS over 15 years at the long-term follow up of the PRISMS cohort, of those patients who return for follow-up visits. Although a direct comparison cannot be made, in natural history data in patients with MS half of patients progressed to SPMS 10 years after onset of disease.[2,19]

Rebif® in clinically isolated syndrome (CIS)

Clinically isolated syndrome is defined as one attack (relapse/exacerbation) with objective clinical evidence of one lesion).[30] In the pivotal REFLEX study, Rebif® 44 mcg significantly delayed progression to McDonald 2005 MS (HR 0.49 [95% CI 0.38–0.64]), the primary endpoint and clinically definite MS (HR = 0.48 [0.31–0.73]), a secondary endpoint, at two years compared with placebo.[6 ,59] People with CIS who are at high risk of conversion to MS should have the option of beginning early treatment with a DMT if they wish to, within the licensed indication.

The definition of MS (McDonald criteria) changed in 2010 to include patients with development of lesions indicative of MS (lesions as shown by MRI in addition to at least one clinical sign indicative of MS).[30]

Therefore, CIS studies such as REFLEX may have included some patients who would now have a diagnosis of multiple sclerosis. Freedman et al conducted a post-hoc analysis of the REFLEX study, addressing this, updating of the definition of MS.[31] A simulated retrospective diagnosis at baseline of dissemination in time and space according to the McDonald 2010 MS criteria, was conducted for each patient. All subgroup analyses were considered to be exploratory.

In general, the treatment effects of Rebif® were similar between predefined subgroups and similar to those found in the overall ITT population: McDonald 2010 MS was retrospectively diagnosed in 37.7 % of patients at baseline.

Both regimens of Rebif® significantly reduced the risk versus placebo of McDonald 2005 MS and CDMS, irrespective of McDonald 2010 status at baseline (risk reductions between 29% and 51%).[31] The effect of Rebif® was not substantially influenced by baseline patient demographic and disease characteristics, or baseline presence/absence of McDonald 2010 MS. This evolution in the definition of MS has been accounted for in the CIS cost-effectiveness analysis presented in this submission.

Rebif® in secondary progressive MS (SPMS)

Rebif is indicated for patients with SPMS if they have ongoing relapse activity. In the SPECTRIMS study,[7] the relapse rate in SPMS patients was reduced from 0.71 per year with placebo to 0.50 per year with treatment ($P <0.001$ for both doses). The hazard ratio for time to progression for the combined Rebif® groups compared with placebo was 0.74 among those patients reporting relapses in the 2 years before study ($P=0.055$), that is, the likelihood of progression was 26% lower in these patients over a 3-year period.

Rebif® has a well-established safety profile and innovative, user-friendly administration technology

Rebif® has a well-established safety profile with an estimated over 1.35 million patient-years of treatment exposure during trials and real-world experience.[8] The most common adverse events are flu-like symptoms and injection site reactions;[28] these are generally mild to moderate and usually diminish with time on treatment.[28]

Adherence to DMTs in MS is variable,[32] but studies show high adherence to Rebif® with RebiSmart®.[33-35] Poor adherence may also be associated with cognitive impairment, as commonly seen in people with MS.There is historical evidence that better adherence to DMTs is associated with better clinical and economic outcomes.[32]

Most patients treated with Rebif® administer treatment via a digital device (RebiSmart®) that keeps records of injections automatically on the device and in addition offers remote monitoring of adherence by healthcare providers.[35-37] At the earliest signs of poor adherence, the healthcare provider can intervene to help the patient adhere to treatment; good adherence ensures the maximum benefits are gained from treatment, giving maximum value from the use of NHS resources. Merck also provides a variety of patient support services including Rebif-device training for patients in the home setting, a website and a helpline staffed by qualified nurses. These value-added services supplement those provided by the NHS.

Access to Rebif treatment and MS Services® on the NHS

Rebif® is currently available on the NHS throughout the UK through the Department of Health Risk-sharing Scheme (RSS), which was set up in 2002 to demonstrate the cost-effective provision of the four DMTs available at that time. The scheme facilitates access to these treatments for all people with RRMS who are eligible under guidelines produced by the Association of British Neurologists.[38] Merck and the other manufacturers have made substantial investments in infrastructure that benefits all MS patients in the UK, most notably the training and funding of MS Specialist Nurses.

Cost-effective provision of Rebif® in the NHS

Under the RSS, over 4000 people were assessed as eligible for treatment and were followed up in a 10-year observational study. At the 10 year timepoint, Rebif® has met its target commitments (hazard ratio)[10] and no price adjustment has been required.

In accordance with the appraisal scope issued by NICE, our economic analysis is based on the RSS model and data. Alongside analyses based on an unmodified RSS modelling approach, we present analyses with an alternative approach to the modelling of mortality. This alternative approach is comparable to that adopted in more recent appraisals, whereby MS related mortality is captured by application of standardised mortality ratios (SMRs) that increase with increasing severity as represented by EDSS. In the RSS model MS mortality is negligible in terms of EDSS levels below 9. Consequently, though the RSS approach employs an arbitrary assumption of a general SMR of 2 across all levels of EDSS, in recognition of expected higher mortality in MS patients, the implications for incremental costs and outcomes of increasing mortality at higher EDSS levels may be very different from models based on SMRs by EDSS. While several alternative data sources for a variety of parameters can be explored in sensitivity analyses, given the important structural difference between the RSS approach to mortality and that based on SMRs by EDSS categories, we present analyses (including the range of sensitivity analyses) based on both.

At the inception of the RSS, it was recognised that for the scheme to operate, a figure needed to be set, under which acquisition of the DMTs could be considered cost-effective. As outlined in the Health Services Circular,[9] a number of factors were highlighted and considered to be relevant to the cost-effectiveness. These were outlined by NICE in the original (2001) TA 32 Final Appraisal Determination (FAD), which specifically referred to two unquantified factors: the impact of treatment on the severity (independent of the frequency) of relapses, and the possible cost offsets from the avoidance of severe levels of disability requiring intervention by the Personal Social Services. In the light of these considerations the threshold was set, for the purpose of the scheme, at £36,000 per QALY. The target outcomes (hazard ratios for sustained disability progression) were agreed for each product included in the scheme based on this threshold, though the DMTs' performance was then assessed in terms of the 'deviation' measure (expected versus actual quality of life weighted EDSS scores). Target hazard ratios are adjusted to account for any residual deviation.

The RSS has concluded that the final hazard ratios for sustained disability progression with the Rebif® 44 and 22 mcg doses are [redacted] and [redacted] respectively, – that is, the likelihood of progressing whilst being treated with Rebif® is over [redacted] lower than would be expected without treatment. The recommended dose of Rebif® is 44 mcg; the lower dose of 22 mcg is licensed for patients who cannot tolerate the higher dose in the view of the treating specialist. We therefore present a principal analysis based on the weighted average of the numbers of patients recorded as taking the 44 and 22 mcg doses in the RSS, considered to be a reasonable reflection of these two doses in real life.

Cost-effectiveness results are shown below for the RSS population based on these hazard ratios, and for SPMS and clinically isolated syndrome based on the SPECTRIMS trial's relapsing population and the REFLEX study of conversion to McDonald criteria MS, respectively. Analyses are presented based on the RSS cost-effectiveness model as at the 10 year analysis, and with modification to model MS mortality based on SMRs by EDSS category, rather than the absolute elevated risk applied in the RSS model for EDSS 9.

Merck converted the RSS model to make it capable of probabilistic analysis, and the results below indicate notable non-linearity. This will in part be due to the RSS approach to mortality (which is not accounted for probabilistically), but also to skewness in costs (to which analyses are generally sensitive), and other parameters.

No acquisition cost budget impact model (BIM) has been submitted with this dossier, as Rebif® has been made available by the NHS since the introduction of the RSS in 2002 (and has been used as the standard of care in subsequent NICE technical appraisals). There are therefore no new funding implications associated with patients' having continued access to Rebif®.

Table 1 Summary of cost-effectiveness analyses in three indications

				[redacted]			[redacted]
		Δ costs (£)	Δ QALYs	ICER	Δ costs (£)	Δ QALYs	ICER
RSS population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SPMS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CIS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Conclusion

Long-term follow-up of pivotal trials and of real-world studies, including the UK Risk-share Scheme have demonstrated the efficacy of Rebif® in reducing relapses and delaying disability progression. Rebif® has also demonstrated an acceptable risk:benefit profile in over 20 years of clinical trials and real-world experience with an estimated over 1.35 million years of patient exposure.[8]

Rebif® has been assessed through the long-term observational study in the UK known as the Risk-sharing Scheme and its efficacy has been scrutinised consistently throughout the scheme. Against the RSS threshold, using the RSS economic model and outcomes, Rebif® can be determined as a cost-effective use of NHS resources compared to best supportive care, and should remain funded in the NHS.

It is important that there is a sustained funding mechanism for people with multiple sclerosis to continue to have access to Rebif® as part of a range of DMTs from which they and their physicians can choose. Reflecting widespread opinion, the Association of British Neurologists guideline[39] states that: "It is essential that MS specialist neurologists can prescribe the full range of available licensed treatments according to what is clinically appropriate and best meets individual needs."

Executive Summary

Multiple sclerosis (MS) is a neurological disease that imposes a considerable burden on patients, healthcare systems and society as a whole.[1,2] People with MS have a health-related quality of life (HRQoL) that is around a third lower than that of the general population,[3] and experience debilitating symptoms, such as fatigue and depression, that considerably impact daily living and activities.[1,4] Epidemiological studies show that MS has an estimated prevalence of 167 *per* 100,000 in the UK in 2010,[5,6,7] and this is increasing.[7,8,9,10] This rate produces an estimated population living with MS in England and Wales of just under 100,000. The overall cost of MS in the UK was estimated to be £2.3 billion in 2010.[11]

Relapsing forms of MS make up over 80% of cases at diagnosis,[12] and includes all forms of the disease where relapses are a feature.[13] The most significant for this appraisal is relapsing-remitting MS (RRMS), which is estimated to account for about 50% of MS cases.[14,15,16] Within the UK, the Association of British Neurologists (ABN) recommendations form the basis for prescribing of MS treatment.[17] These guidelines recommend treatment for RRMS only if the disease is active or meets the 2010 McDonald criteria.[18]

The definition of clinically isolated syndrome (CIS) was revised in the 2010 update of the diagnostic criteria, and diagnosis of MS can occur after a single neurological event with supporting magnetic resonance imaging (MRI) results.[18] This has led to many cases historically diagnosed as CIS now being classified as MS. Prior to these changes, CIS accounted for approximately 2-3% of the overall MS population.[14] Under the updated diagnostic criteria (2010) the incidence of CIS has reduced considerably, but there are no available population estimates. Treatment is only recommended for CIS if there is a significant risk of developing MS.[17] These changes mean that CIS is not a significant indication for MS therapies and, as a result, has not been included as the primary focus of this submission.

Copaxone® (glatiramer acetate) has worldwide approval and with decades of use has accumulated more than 2 million patient-years of experience.[19] Copaxone is supplied in pre-filled syringes for subcutaneous injection: Copaxone 20mg/ml once-daily was granted UK Marketing Authorisation in 2000; and Copaxone 40mg/ml three times a week was launched in 2015. The list price and Risk Sharing Scheme (RSS) price, for both dosing regimens of Copaxone, are £513.95 *per* 28 days. The RSS was established to provide patient access to treatment at a cost-effective price to the NHS and to collect data on long-term effectiveness and cost-effectiveness on a cohort of these patients.[20,21] Copaxone is indicated for the treatment of relapsing forms of multiple sclerosis. The Summary of Product Characteristics (SmPC) details the populations in which clinical trials have been conducted: 20mg/ml has been studied in RRMS and CIS (as *per* 2001 McDonald criteria),[22] 40mg/ml has been studied in RRMS (as *per* 2005 McDonald criteria).[23] Copaxone is not indicated in primary or secondary progressive MS.[22,23] The two dosing regimens of Copaxone are clinically equivalent in terms of efficacy and overall safety profiles, as confirmed through clinical trials and regulatory approval.[24,25,26] Clinical equivalence has also been confirmed by UK neurologists within current UK practice.[27] The 40mg/ml dose represents an innovative step forward with respect to a reduced frequency of administration *vs* the 20mg/ml dose and 50% fewer injection site reactions. Relevant approvals for Copaxone 40mg/ml have been received based on submissions that demonstrate the clinical equivalence of these dosing regimens, which includes regulatory approval from the Medicines and Healthcare Products Regulatory Agency (MHRA),[26] and formulary/reimbursement approval from the Scottish Medicines Consortium (SMC).[28] As such, both regimens of Copaxone are presented as a single entity in this submission.

The most important source of data for this appraisal is the UK RSS. The RSS was set up in 2002 and included a 10-year observational cohort specifically to assess the long-term benefits of the then available disease modifying treatments (DMTs), due to recognised limitations in extrapolating from short-term clinical studies.[20,21] There are recognised limitations in extrapolating long-term trends from short-term clinical studies, which was highlighted by the original NICE appraisal on these therapies and something the RSS was, in part, established to address.[20,21] The treatments included in the RSS were Copaxone, interferon beta-1a (both subcutaneous and intramuscular formulations) and interferon beta-1b. The RSS provides cost-effective provision of these DMTs on the NHS, whilst collecting long-term data on their clinical and cost-effectiveness. The primary outcome measures for the RSS are disability progression, as measured by the Expanded Disability Status Scale (EDSS), and the impact of accumulation of disability on patient functioning, recorded as loss of utilities.[29] Since loss of utility represents a functional impact of disability on patients, this was used to drive the cost-effectiveness calculations, rather than the EDSS scores, which were considered a more clinical endpoint. Data on disability progression is particularly important as this outcome requires long-term analysis[13] that has not been carried out in the clinical trials,[30] and is the outcome that most affects long-term cost-effectiveness. The RSS is

the largest prospective, real-world, UK-based study of MS therapies; with access governed by the ABN criteria,[17] it includes UK patients covered by this appraisal and is representative of UK clinical practice. Altogether, these factors underline why the RSS is a hugely valuable and pivotal data source for this appraisal.

The effectiveness of treatments for MS should principally be judged on the basis of reducing disability progression and reducing or preventing relapses. As the RSS is an observational study, a "virtual control group", using data from the British Columbia Multiple Sclerosis database, was used as a natural history comparator. Results from the RSS are presented as implied hazard ratios (HR), which are the HRs required by the RSS model (a continuous Markov model) to produce values that match the observed data. The final, 10-year results using the Department of Health (DoH) supplied model show **Copaxone delivered a reduction in risk of EDSS disability progression** with no evidence of a treatment waning effect compared to the updated 6-year analysis.[i] When the implied HR for EDSS progression are compared to the results for the combined DMTs (including Copaxone) at the 10-year analysis undertaken by the RSS Scientific Advisory Group (SAG), **Copaxone can be seen to have performed better than the combined beta interferons**. Similar trends were also observed in the utilities data collected by the RSS. A multi-level, repeated measures model using the RSS data (developed by SAG) demonstrated a greatly enhanced effectiveness of the aggregate DMTs through EDSS progression *vs* the RSS Markov model.[29,31] This highlights that the RSS Markov model might be conservative in some of its outcomes and that the DMTs in the RSS may be more effective than this model suggests.

The clinical studies for Copaxone (both 20mg/ml and 40mg/ml) provide strong evidence in terms of relapse reduction, whilst providing valuable information on disability and other outcomes, such as lesion activity on MRI.[30,32,33] Studies using a similar methodology and patient populations demonstrate a reduction in annualised relapse rate of between 27.5%[34] and 35.3%[24] for Copaxone *vs* placebo and between 5.6%[35] and 10.8%[36] *vs* beta interferons. Studies have also demonstrated the efficacy of Copaxone using other clinical measures (*e.g.* disability and MRI activity) compared to both placebo and beta interferons.[30,32,33] Network meta-analyses can provide further insight where there is a lack of direct comparative data between drug treatments; however, this approach is limited for the DMTs by significant heterogeneity across studies in terms of differing patient populations, the changing natural history of MS, and variability in how outcomes were defined and recorded.[30,37] Despite these caveats, meta-analyses show that Copaxone compares favourably with the beta interferons, having at least equivalent efficacy in RRMS.[30,32] Real world studies have shown the effectiveness of Copaxone in terms of patient functioning and quality of life (*e.g.* fatigue, ability to work).[19,38,39] Copaxone has been shown to significantly improve symptoms of fatigue compared with beta interferons,[19] with fatigue being frequently reported as one of the most debilitating symptoms of MS.[1] **Overall, Copaxone has been shown to be highly effective therapy for RRMS**.

Copaxone has a well-established safety profile and has been shown to be a well-tolerated treatment during over 20 years of usage.[17,30] Copaxone has been associated with no emergent safety signals (unlike beta interferons)[40] and has no specific monitoring requirements.[22,23] Comparatively, the safety profiles of Copaxone 40mg/ml and 20mg/ml are similar; with Copaxone 40mg/ml demonstrating reduced injection site reactions due to its reduced dosing requirements.[25] Additionally, Copaxone can be used in people with RRMS where beta interferons are contraindicated or not considered an appropriate treatment option, for example, in those with significant depression.[41] Copaxone is associated with a low incidence of flu-like symptoms, a particular problem with beta interferon therapy,[30,42] and one that can affect adherence to therapy.[43] Copaxone also does not cause the production of neutralising antibodies (NAbs), unlike beta interferons.[42] NAbs generally develop soon after the initiation of therapy, and in most cases within 18 months.[44] NAbs are known to be detrimental to therapeutic effects in terms of relapses, disease activity on MRI, and disease progression.[44] Therefore, guidance states that NAbs should be routinely tested,[44] and that the development of NAbs may necessitate switching to a second-line DMT.[44] However, testing of NAbs is not routinely carried out within UK practice,[45] which may mean that patients on beta interferons remain on a sub-optimal treatment for a long period of time, leading to inferior outcomes.

The cost-effectiveness of Copaxone has been demonstrated by two different models. The most relevant, real world, cost-effectiveness data come from the RSS, with the modelling refined throughout the 10 years of the scheme. The final analysis methods have been agreed by the DoH and the RSS SAG. Each treatment in the RSS was assigned an individual

[i] Updated 6-year analysis uses updated 6-year RSS data with the most recent 10-year model. Minor changes have been made to the analysis at 10-years that include the inclusion of EDSS scores recorded after a switch to a non-scheme DMT (originally these were censored at change) and changes to methods for imputation of missing data values (using later values for missing earlier ones).

target reduction in EDSS worsening, predicated on data from its registration studies. The strong performance of Copaxone, in comparison to its target, at the 6-year analysis of the RSS led to it being granted a price rise to full list price starting from January 2015. The modelling of cost-effectiveness in the RSS is based on the accumulation of disability measured through utilities and uses a Markov model. For Copaxone in the DoH agreed analysis, this produces an incremental cost-effectiveness ratio (ICER) *per* quality-adjusted life year (QALY) *vs* best supportive care that shows Copaxone is a highly cost effective treatment. Sensitivity analyses have demonstrated the robustness of the model.

The cost-effectiveness of Copaxone can also be demonstrated based on a network meta-analysis of clinical trial data. This approach is recognised to be significantly limited by the available clinical trial data in MS; particularly by the heterogeneity between the study populations and by the weakness in disability progression data from short-term trials. A *de novo* Markov model was developed by Teva, based on the RSS model, but extended to include additional important factors that affect cost-effectiveness (such as NAbs and second-line treatment). This model produced an ICER *per* QALY for Copaxone *vs* best supportive care that again shows that Copaxone is a highly cost-effective treatment. Sensitivity analyses have demonstrated the robustness of these findings. Using this model to compare DMTs revealed that Copaxone shows strong cost-effectiveness over the beta interferons. The only exception is pegylated beta interferon, but this was based on the results of a single, short (one-year) clinical trial which had disability progression as a secondary outcome and a study population not reflective of the UK MS population.[46] Without strong evidence otherwise, pegylated beta interferon must be assumed to be clinically equivalent to the other beta interferons. Altogether, these results show that different modelling approaches and different data sources consistently demonstrate that **Copaxone is a highly cost-effective option for the treatment of MS, which compares favourably to the beta interferons**.

Overall, the data presented show that Copaxone is proven to be effective and of real benefit to patients with RRMS. Copaxone has been shown to be efficacious in the RSS and randomised, controlled trials, with a low level of adverse events that can be easily managed; with results backed up in clinical practice from more than 20 years of use and no evidence of treatment waning. Copaxone has been consistently shown to be cost-effective using two different cost-effectiveness models. In all of these areas, Copaxone compares favourably to the beta interferons. **Copaxone should therefore be considered as the first choice treatment for relapsing forms of MS, due to its efficacy, proven safety profile, innovation, and cost-effectiveness ahead of beta interferons**.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (MTA)

Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment(s).

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to say which treatment (s) you are commenting on.

1. About you and your organisation

Your name: [redacted]
Name of your organisation: Multiple Sclerosis Society
Your position in the organisation: [redacted]
Brief description of the organisation:

The MS Society is the UK's largest charity for people living with Multiple Sclerosis (MS), with approximately 38,000 members and 300 branches across the country. We are the UK's largest charitable funder of research into MS. Since 1953 the MS Society has been providing information and support for people affected by MS.

The MS Society funded its first research project in 1956 and we continue to fund research into both disease modifying and symptom management treatments. We also provide grants to individuals, for example in order to make home adaptations. We are committed to bringing high quality standards of health and social care within reach of everyone affected by MS.

While we work towards a cure, we will continue to fight the corner for people affected by MS – demanding the highest quality care and support, wherever they live in the UK.

This submission has been prepared by the MS Society's Policy and Research directorate and is informed by:

- The most recently published results from the Risk Sharing Scheme
- Clinical trial data (please see appendices for extensive table)
- Various research on perspectives, including:
    - Case studies of first hand experiences from people who have or are taking these treatments – collected by the MS Society for this submission by inviting comments from our supporters
    - The MS Society's 'Right Treatment, Right Time? How people with MS make decisions about disease modifying drugs' 2014
    - The MS Society's 'Perspectives of people with MS on relapses and disease modifying drugs' 2010
    - Other relevant perspective papers listed under 'relevant studies section'.

The following appendices are attached to this submission:

- Appendix A: A table of relevant clinical trials including brief descriptions of their findings
- Appendix B: A report on the perspectives of people with MS on relapses and disease modifying treatments

Executive Summary

Numerous clinical trials showing the effectiveness of these disease modifying treatments (DMTs) are now supported by the long term data results of the

Risk Sharing Scheme (RSS). The DMTs have been shown to be effective in reducing relapses and slowing the progression of MS. As these DMTs have been widely available since 2002 in the UK (and are now widely available in all developed countries) for people with MS (pwMS) there is significant evidence to attest that they have a good safety profile. It is crucial that these treatments continue to be available on the NHS, offering a diversity of choice to pwMS. This diversity, alongside patient education and clear criteria on available treatments, will ensure more people make an effective shared decision with their clinician on which DMT is best suited for their MS. Greater support and choice of DMTs offered to pwMS will help achieve greater cost effectiveness in treating MS overall.

While for some pwMS side effects experienced when administering these DMTs have acted as barriers to treatment, there have been significant technical developments in the routes of administration. Improvements in the delivery mechanisms and the frequency of administration have made beta interferons and glatiramer acetate more user friendly than when first available.

More widely these treatments have improved quality of life for pwMS and saved the NHS and social services money.[1]

Efficacy of Treatments

Beta interferons and glatiramer acetate have a long history of use as MS treatments. The US Food and Drugs Administration (FDA) first approved these DMTs during the early to mid-nineties. In trials and follow up studies, the treatments have been shown to be moderately effective in both reducing relapses and slowing disability progression. It is estimated that relapse rates for people taking beta interferons reduce by an average of 33% compared to the placebo groups, while relapse rates for people taking glatiramer acetate dropped an average of 34%.[2] These represent a significant improvement compared to how MS progresses without DMT intervention.

Since the pivotal trials in the eighties and nineties, there have been a number of more recent trials which have further tested the efficacy of treatments. There have also been tests against comparator treatments, trials into new delivery options and reviews of how those from the original trials have progressed since.[3] These clinical trials provide robust clinical evidence that these DMTs are effective over the long term and benefit pwMS greater the earlier they are taken.

Improved understanding of disease activity and measurements of damage caused by MS have led to the scientific consensus that the earlier treatments

[1] All treatments have been shown to reduce relapse rates which have a substantial impact on pwMS's quality of life and ability to engage in society. This is further unpacked in the 'advantages' section of this paper.

[2] For beta interferons see PRISMS and ADVANCE trials in appendix A. For glatiramer acetate see GALA Study in appendix A

[3] See appendix A for specific clinical trials comparing beta interferons and glatiramer acetate with other DMTs. Examples include TRANSFORMs & CARE MS

are deployed the greater the long term efficacy (see the Brain Health report,[4] and US consensus paper by the MS Coalition,[5] and the MS Society consensus paper,[6] for more information). A trial comparing beta interferon with alemtuzumab[7] found that interferons perform better than in previous trials when early adoption is instigated. This understanding means that these DMTs adopted early have a significant potential to have a greater impact in reducing disease progression than shown in the pivotal trials.

Risk Sharing Scheme

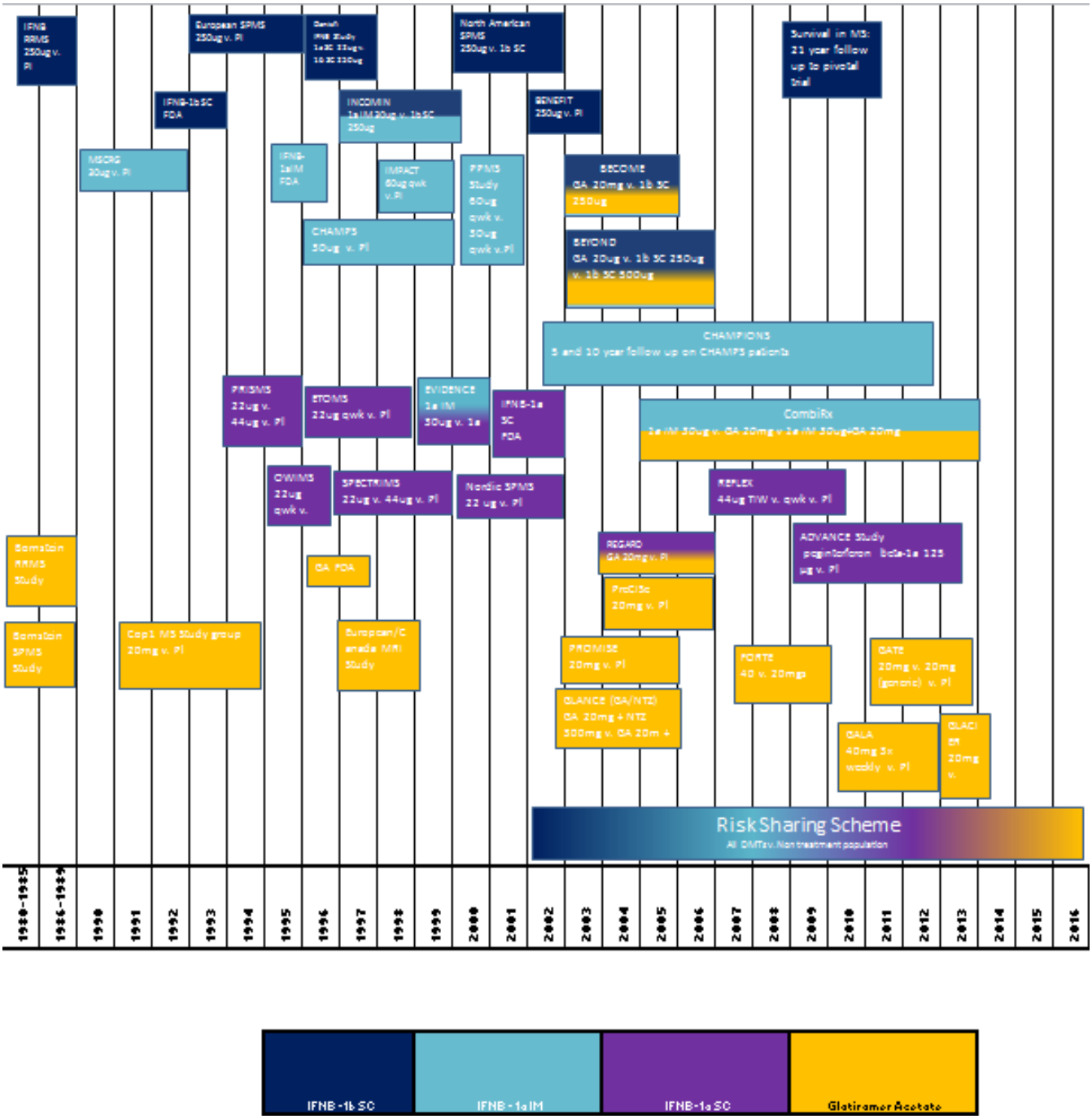
The latest published results from the RSS have shown that beta interferons and glatiramer acetate are cost effective over the long term, providing the best available observational data on whether these DMTs change the natural progression of MS.[8]

In 2002, the DMTs were found to be cost effective in a NICE multiple technology appraisal but only on the condition that the short term disability benefits reported in clinical trials could be maintained over the longer term. The UK RSS was established to assess whether disability progression would be consistent with a cost effectiveness target of £36,000 per quality adjusted life year projected over 20 years.

The year 6 results of the RSS published in the Lancet in April 2015 have established that the treatments are cost effective over 6 years.[9] This analysis used two models to examine the disease progression of UK participants in the RSS against a control group of pwMS from Canada. The findings provide observational data that the DMTs were within the cost effectiveness target of £36,000 per QALY exceeding the requirement.

Table of Clinical Trials and Observational Studies of Beta Interferons and Glatiramer Acetate (excluding numerous comparison trials with other DMTs)

[4] Giovanni et al, 'Brain health: Time Matters in Multiple Sclerosis', Oxford PharmaGenesis Ltd, 2015
[5] The Use of Disease Modifying Therapies in Multiple Sclerosis: Principles and Current Evidence. A Consensus Paper by the Multiple Sclerosis Coalition, updated March 2015
[6] Time to act – a consensus on early treatment, MS Society, 2015
[7] Cohen et al, 'Alemtuzumab versus interferon beta 1a as first line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial, Lancet, 24;380(9856):1819-28, November 2012
[8] Palace et al, Effectiveness and cost-effectiveness of interferon beta and glatiramer acetate in the UK Multiple Sclerosis Risk Sharing Scheme at 6 years: a clinical cohort study with natural history comparator, Lancet, Volume 14, No. 5, p497–505, May 2015
[9] Ibid



Key concluding messages

The evidence from clinical trials and the RSS has proven beta interferons and glatiramer acetate are all clinically and cost effective compared to best supportive care. Though they have less efficacy than some of the newer treatments now available, they are an important option for pwMS, promoting informed patient choice so that people who are less inclined to take risks with their treatment option can choose a DMT with a reliable safety record and proven efficacy. This is a particularly important option as within MS DMTs, the general rule is that the higher the efficacy of the treatments, the greater the risk of side effects.[10] The greater the range of DMTs available means that

[10] Time to act – a consensus on early treatment, MS Society, 2015

more people are likely to find the treatment that suits them. If these DMTs were no longer available on the NHS, it would be likely to result in less people being effectively treated for MS.

The Association of British Neurologists (ABN) specifically recommends beta interferons and glatiramer acetate for 'individuals with relatively quiescent disease'.[11] They also highlight the safety profile of these DMTs, which have been available on the NHS through the RSS since 2002, as meaning they provide an effective treatment for the '*more risk averse'*. This has been backed up in the case studies gathered by the MS Society (to inform this submission); several responders commented on feeling most comfortable with the known risks of the more established DMTs opposed to newer, riskier DMTs. MS varies in how it affects people, and how people choose to treat it. For those who are averse to the greater risk involved with newer treatments, these beta interferons and glatiramer acetate offer options with a known low level of risk and moderate effectiveness.

The UK currently has one of the lowest prescribing rates for MS DMTs in Europe.[12] The MS Society is deeply concerned about the following implications should the treatments no longer be available on the NHS:

- Those currently taking the treatments would lose access to the DMT which they have found best works for them and have less choice of treatments

- Loss of treatment options could potentially lead to people deciding not to take any DMTs (particularly affecting pwMS who are more risk averse)

- Fewer people will receive treatment that works for them – many may not be treated at all, with negative impacts on their health

- PwMS would be at increased risk of falling out of employment due to relapses and disability progression, resulting in greater reliance on welfare support (research shows that employment rates go down the longer people have had MS).[13]

- PwMS would be more reliant on carers and therefore less independent (currently 71% of pwMS rely on unpaid support).[14] PwMS would be less able to undertake basic tasks associated with daily living and would feel physically limited by their condition as their MS progressed faster; carers would also be likely to experience poorer health and a loss of quality of life.

[11] Scolding et al, Association of British Neurologists: revised (2015) guidelines for prescribing disease modifying treatments in multiple sclerosis, *Pract Neurol* doi:10.1136/practneurol-2015-001139

[12] A lottery of treatment and care – MS services across the UK, MS Society, 2013

[13] New MS Register data gives insight into employment and depression levels, MS Society News, 2012

[14] A lottery of treatment and care – Ms services across the UK, MS Society, 2013

- Care and support costs met by the NHS and social services will be higher. The more pwMS experience relapses and the resulting disability associated with it, the more pwMS will increase their reliance on NHS and social care services (a survey by the MS Society found that 91% of people felt they had to rely on other people at least occasionally after a relapse).[15]

- PwMS will experience poorer emotional wellbeing/mental health. Currently two thirds of pwMS experience anxiety and/or depression, to a level requiring clinical intervention.[16]

These arguments are further elaborated on with supporting evidence in this submission.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

MS is one of the most common disabling neurological conditions affecting young adults. Around 100,000 people in the UK have MS. MS attacks at random with many of the symptoms invisible to others. It affects almost three times as many women as men and people are usually diagnosed in their 20s or 30s; news that can be scary and difficult for people to adapt to. Although much progress has been made in identifying DMTs, these are not curative and even the most effective carry significant risks for pwMS.

Relapsing remitting MS (RRMS) affects around 85 per cent of those diagnosed with MS. A relapse is defined as an episode of neurological symptoms, which lasts for at least 24 hours and occurs at least 30 days after the onset of any previous episode. In relapses, symptoms usually come on over a short period of time but often remain for a number of weeks – usually three to four – and can sometimes last for months.

Our understanding of how MS attacks the body is changing. MS specialists used to think that once a relapse was over, the damage to your brain and spinal cord stops and no new damage was happening. But now we know that even when you are not having relapses MS can still be causing damage. This damage can be happening even if there are no visible signs of it, such as a relapse. That's why early treatment with a DMT is now considered to be the best method of slowing the disability progression.

[15] MS Society's 'Perspectives of people with MS on relapses and disease modifying drugs' 2010, Appendix B

[16] Jones et al, A large scale study of anxiety and depression in people with MS: A survey via the web portal of the UK MS Register, 2012.

PwMS can experience a wide range of distressing and debilitating symptoms from fatigue to visual impairment, mobility problems to cognitive problems. Relapses can vary from mild to severe, with 95 per cent of pwMS feeling relapses left them unable to do the things they wanted to do.[17] At their worst, acute relapses may need hospital treatment, but many relapses are managed at home, with the support of a GP, MS specialist nurse and other healthcare professionals. Although some people recover from relapses and experience complete remission, around half of all relapses leave residual problems; another important reason to reduce the frequency and severity of relapses. New evidence has highlighted that disability also progresses regardless of whether a person experiences relapses regularly.[18]

Due to the varied and unpredictable nature of MS, determining an 'average; relapse rate is not straight forward; considering the number of people currently on disease modifying drugs it is estimated that a significant proportion of individuals with RRMS experience one or more relapses a year.
Relapses can have a resonating emotional impact on a person, the loss of independence that can often come with a relapse mean that people can often feel a burden on their family (93 per cent). Relapses are often unpredictable and distressing, leaving most people feeling frustrated (80 per cent) and anxious (67 per cent) and causing a disruption to a person's everyday life.[19]

The majority of pwMS experience a progression of disability over the course of the condition. It is estimated that approximately 65 per cent of people with RRMS will eventually go on to develop secondary progressive MS 15 years after being diagnosed and 10-15 per cent are affected by primary progressive MS. Progressive forms of MS are characterised by a sustained accumulation of disability independent of relapses. This progression occurs at varying rates and can lead to a worsening of symptoms resulting in a permanent loss of mobility and the need to use a wheelchair, cognitive damage and permanent sight loss. There is also a real risk of accumulating disability for those with RRMS who are refractory to first line treatment.

The MS Society knows tackling disability progression is a major issue for pwMS and currently represents an unmet treatment need. Our new Research Strategy (2013-17) highlights research into progression as a major priority for the MS Society going forward. The strategy was formed in consultation with people affected by MS and the MS research community. It was approved by our Board of Trustees - the majority of whom are people affected by MS, either directly or as carers. Proving DMTs slow disability progression is notoriously difficult; but without at all minimising the difficulty of living with relapses, a product that has shown significant benefit here would be greatly valued by people affected by MS. The potential to maintain function and have a greater quality of life is of critical importance, especially for a chronic, long-

[17] MS Society's 'Perspectives of people with MS on relapses and disease modifying drugs', 2010, Appendix B
[18] Giovanni et al, 'Brain health: Time Matters in Multiple Sclerosis', 2015
[19] MS Society's 'Perspectives of people with MS on relapses and disease modifying drugs', 2010, Appendix B

term and potentially debilitating condition such as MS that so often evolves from relapsing-remitting MS to the secondary progressive phase.

PwMS live with great uncertainty, not knowing from one day to the next whether they will be able to move, to see or to live even a remotely normal life.

Impact on Carers
In a survey of over 10,000 members of the MS Society with MS, 71% of respondents received unpaid care, support or assistance from a friend of family member.[20] Carers of pwMS are not getting the support they need. Just 45 per cent of pwMS who feel that their carer needs a carers' assessment were offered one; and for those who are really struggling financially this falls to just 37 per cent.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

There are currently 11 DMTs available on the NHS in the UK, offering pwMS a variety in treatments, that, until recently did not exist. In the 'Right treatment, right time' survey carried out by the MS Society in 2014, those who responded to the questionnaire identified stopping further relapses as the most important reason to start taking DMTs (93%), followed by 84% who hoped it would reduce the severity of their relapses, and 84% who hoped it would result in less disability over the long term.[21] It is important to reiterate that relapses are not the only signifier of disability progression in RRMS. People's disability often progresses between relapses so while these outcomes focus on different aspects of MS, they are all interconnected.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these different treatments and which are preferred and why?

The MS Society offer support and information for pwMS on all the treatments currently available. We also have provided information to NICE on previous appraisals.

There are currently 11 DMTs available through the NHS. Of these DMTs alemtuzumab and natlizumab are classified as 'high efficacy' by the Association of British Neurologists (ABN). The remaining DMTs: beta interferons, glatiramer acetate, teriflunomide, dimethyl fumarate and fingolimod are classified as 'moderate efficacy' drugs. Within the moderate efficacy classified DMTs, dimethyl fumarate and fingolimod are considered the most effective, however as the ABN guidelines highlight:

[20] A lottery of treatment and care – MS services across the UK, MS Society, 2013
[21] Right treatment, right time? How people with MS make decisions about disease modifying drugs, MS Society, 2014

'beta interferons and glatiramer acetate have been used extensively for decades in MS, and there is a wealth of clinical experience confirming their general safety. Individuals with relatively quiescent disease and/or who are more risk averse might therefore be more likely to choose one of the beta interferons or glatiramer acetate'

Beta interferons and glatirmamer acetate also offer a treatment option which can be taken up to the point of conception.[22] For pwMS who are planning a family this means that they are able to stay on medication for as long as possible – other DMTs are advised to be discontinued months before conception.

Decisions on which DMT to take are determined by a variety of factors including the efficacy, related side effects, the method and frequency of taking, and lifestyle factors. A survey carried out by the MS Society found that the majority of people (95 per cent) preferred the option of a pill (a preference backed up by a number of other surveys),[23] giving ease of use, [24] convenience to everyday life and non-invasiveness as reasons for selecting this option. There was also a clear preference for options which would allow pwMS to be in charge of their own treatments.

The MS Society have also found that there is a lack of understanding and communication about what treatment options are currently available, with one in five people having not heard of any DMTs, or only heard of just one, as found in a 2014 survey.[25] While MS nurses and neurologists are reported to be the most useful sources of evidence in aiding people to make a DMT decision, our research has shown that 20 per cent of people had not met with a neurologist and 16 per cent had not met with an MS nurse within a 12 month period.

4. What do patients or carers consider to be the advantages of the treatment(s) being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)

[22] Vukusic et al, Multiple Sclerosis and pregnancy, Revue Neurologique, Volume 162, Issue 3, Pages 299–309, March 2006
[23] Please see 'relevant survey' section for details of further surveys on patient choice
[24] Right treatment, right time? How people with MS make decisions about disease modifying drugs, MS Society, 2014
[25] Ibid

- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment(s) being appraised.

Beta interferons have been shown in clinical trials to have a moderate level of efficacy with relapse rates dropping on average by 33% and slowing disability progression by modest levels. The results of the risk sharing scheme have since confirmed that disability progression is slowed over a 6 year period with a trajectory that means the DMTs are cost effective over a 20 year period, (exceeding the minimum cost effectiveness requirements).

Another study of pwMS looking at the effects of interferon beta 1b on mortality over 21 years found that there was a significant advantage in the cohort who had received earlier treatment at either of the doses examined compared with placebo. [26] With the hazard rate of death at long term follow up reduced by 46.8% compared with placebo. This is a hugely significant finding which highlights both the importance of early treatment and the need for people to continue accessing these DMTs.

These treatments offer pwMS the opportunity to reduce the number of relapses and disability progression while providing a reassuring safety record. When compared to best supportive care these DMTs have a hugely positive impact on a person's life, reducing the need for social care and aiding people to stay fully engaged in society.

As the DMTs in this appraisal have been widely used by pwMS for over a decade there is a wealth of knowledge and experience of the advantages and disadvantages of taking them. The MS Society asked supporters to get in touch with their experiences, asking for them to describe what influenced their decision to take one of these DMTs and what the positives and negatives experienced were. The feedback consisted of over 200 case studies highlighting a number of areas where these treatments have benefited pwMS. Key themes with supporting quotes are examined below (contributions referenced as case studies).

A lower annualised rate of relapse

Since the pivotal clinical trials in the late eighties and early nighties, there have been a number of follow up trials into beta interferons and glatiramer acetate (including trials to explore the effectiveness in combination treatments and follow up trials of the original participants) which have established a

[26] Goodin et al, Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFNβ-1b trial. Neurology, 78(17):1315-22, April 2012

statistically significant reduction in relapses averaging at 33% for beta interferons and 34% for glatiramer acetate. [27]

Case studies:

'I had only two significant relapses in the 11 years I was on Copaxone, compared to roughly once every six months before taking it, I felt it had a hugely positive effect in my life'

'I had relapsed three times in six months before I went on Avonex and since I started the injections two and a half years ago, I've been relapse free'

'The advantages have been that since taking beta interferon, I have had no further relapses and although I still have the trigeminal neuralgia, I have had no further long term symptoms in approximately 4 1/2 years.'

'The key thing is that I have not had a relapse since taking Rebif and as my usual relapse pattern seemed to be every 2-3 years, I am truly amazed that I have not had a relapse in nearly 7 years! I am very impressed and grateful for my treatment!'

As previously stated, pwMS report relapses having a hugely disruptive impact on their lives. These treatments have provided people with an option for reducing these disruptions.

Reduction in risk of confirmed progression of disability

The RSS was established to test whether these DMTs would have an impact on disability progression over a long term period. On this scheme, between 14th January 2002 and 13th July 2005, 5610 people from 72 UK sites were enrolled. The scheme looked at the accumulation of disability using the Expanded Disability Status Scale (EDSS) to quantify the progression and loss of utility. The RSS also utilised two different models for analysing the date. For both outcomes, pwMS in the RSS progressed more slowly than predicted from natural history models with an observed reduction in disability progression of 24.2% and 40 % in the two models used to analyse the year 6 data. [28]

With the year 10 data due out this year, the RSS represents the best study of disability progression for the appraised DMTs. This is a factor that deserves attention as the clinical trials predominantly took place over two years with relapse as their main focus. The systematic review of clinical trials undertaken by the Cochrane Collaboration to evaluate the ability of these DMTs to reduce disability progression is limited by the fact that it does not acknowledge that the majority of trials were not examining long term efficacy. It also does not

[27] For beta interferons see PRISMS and ADVANCE trials in appendix A. For glatiramer acetate see GALA Study in appendix A

[28] Palace et al, Effectiveness and cost-effectiveness of interferon beta and glatiramer acetate in the UK Multiple Sclerosis Risk Sharing Scheme at 6 years: a clinical cohort study with natural history comparator, Lancet, Volume 14, No. 5, p497–505, May 2015

take into full consideration the current scientific consensus on the importance of early treatment. The review highlights the need for long term studies to draw more significant conclusions, of which the RSS is the best example to date.

Case studies:

'I believe it has made a huge difference to my life in that it has slowed down the progress of the disease.'

'It was daunting at first, I was worried about side effects on top of the daily MS symptoms, but after a week or two, I felt the difference to my MS, it really slows things down'

Early Treatment

The need for early treatment in MS has recently been highlighted (see the Brain Health report and US consensus paper by the MS Coalition as well as the MS Society consensus report for more information). [29] The scientific consensus now is that the earlier DMTs are taken by pwMS the slower the disease progression. Trials, such as the Alemtuzumab vs interferon beta[30] have found that both beta interferons are more effective than previous trials suggest when adopted early.

A six year study of patients taking glatiramer acetate concluded that early use of the treatment has a bearing on efficacy, with those taking treatment (rather than placebo) from the outset being less likely to be using a walking aid at six years. [31]

A long term follow-up trial of the early pivotal interferon trials reveals interesting data. Within this trial the placebo group was switched to active treatment after three years.[32] The 16 year data showed significantly improved physical and mental outcomes for those receiving the treatment from the outset compared with those in the placebo group. A further paper was published in 2012, showing an even more stark difference in outcomes between the two groups for the 21 year follow-up. [33] It showed that people who were given beta-interferon in the original treatment group had a 50% reduction in mortality rates compared with people who started on the placebo and switched to interferon three years later

Impact on Clinically Isolated Syndrome (CIS)

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[29] Time to act – a consensus on early treatment, MS Society, 2015

[30] Cohen et al, 'Alemtuzumab versus interferon beta 1a as first line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial, Lancet, 24;380(9856):1819-28, November 2012

31 Rovaris et al, Long-term follow-up of patients treated with glatiramer acetate: a multicentre, multinational extension of the European/Canadian double-blind, placebo-controlled, MRI-monitored trial, Mult Scler,13(4):502-8, May 2007.

[32] Ebers et al, Analysis of clinical outcomes according to original treatment groups 16 years after the pivotal IFNB-1b trial, J Neurol Neurosurg Psychiatry;81:907e912, 2010

[33] Goodin et al, Survival in MS: A randomised cohort study 21 years after the start of the pivotal IFN beta-1b trial, J Neurology, Vol 78, 17, 2012

As the way MS is diagnosed and first treated is being changed to meet the Macdonald criteria 2010, which considers brain lesions rather than a diagnosis based solely on whether two relapses have been experienced in one year, the potential for these DMTs to slow conversion to MS is considerable.

The Precise trial studied the ability of GA treatment to delay the onset of clinically definite MS (CDMS) in a 36 month, placebo controlled, prospective, randomised, double blind, multi-centre trial. A total of 481 patients with CIS and screening MRI scans with >T2 brain lesions were enrolled. [34] Using an intend to treat analysis, GA reduced the risk of developing CDMS (defined as a second clinical attack) by 45% compared with placebo.

Quality of life (lifestyle, activities of daily living, independence)

These DMTs provide moderate reductions in relapses and disability progression (within the DMT landscape overall), offering pwMS a greater range of treatment options to find what works best for them. The reductions produced by these DMTs have a considerably positive impact on people's lives.

Case studies

'I continue to lead a very active life including swimming and walking several miles a week, doing voluntary work, gardening, playing the piano and craft work.'

'I could live independently and work the best I could, and also, as not many side effects, I could go the gym and keep active.'

Some people commented specifically on choosing Rebif as they feel it is least disruptive to their lives compared to options which involve daily injections. People also commented on the self-administering aspect of treatments meant they could treat themselves '*rather than going into hospital once a month and missing work*'.

Physical Symptoms

Many pwMS who have taken these DMTs feel that they have made a significant improvement in the physical symptoms that can come with MS. As one person commented, they have experienced *'ongoing good health, with only minor and infrequent symptoms'.* Other pwMS commented on the difference before they were taking treatments and what a difference the lessoning of symptoms has made to their lives.

Case studies

[34] Comi, G et al. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo controlled trial, The Lancet , Volume 374 , Issue 9700 , 1503 - 1511, Oct 2009

'I haven't had a relapse in seven years. Before Copaxone, I was relapsing two or three times per year, which had a massive impact on my career and social life (cancelled holidays, etc.). I'm not symptom free, but my symptoms are mostly manageable.'

'Now four years in I rarely have symptoms'

'Easy to use, fortunately haven't suffered with too many side effects as all controlled with paracetamol, haven't had any more known episodes whilst taking Rebif'

Mental Health

Reducing the number of relapses and slowing disability progression has a profound impact on a person's mental health. The emotional and psychological impact of a relapse and increase in disability should not be underestimated. Approximately two thirds of pwMS suffer from depression and/or anxiety due to both the physical changes caused by MS and the strain of living with such physical uncertainty. Suicide is also more common in pwMS than the general population.[35] Alongside this, many pwMS do not get the emotional support that they need, with only 51 per cent of those who needed emotional support able to get it.[36] One respondent provided a useful insight into the emotional impact of a relapse:

'Relapses are not only worrying, painful and distressing at the time but can take a considerable amount of time to recover from. I have been left with residual problems from every relapse I have had and then the worry of if I have another, is the disease progressing quicker than I thought – that is always a worry at the back of my mind. I then worry about the impact on my husband and that he has to take time of work to help me. The concern that he will not cope if I become severely affected by another relapse is a genuine worry as he gets extremely frustrated with the whole MS scenario. As a very independent lady, this adds its own issues to my state of mind and the fact that I cannot be there as readily for my children and colleagues'[37]

Case study:

'Copaxone has helped me feel a little more in control. It can't undo damage done, but it can improve the odds of avoiding future relapses, and so slow down disease progression, which gives me more confidence to go out and do things.'

A number of pwMS also highlighted the positive mental impact that taking a DMT had on them, commenting on the importance of feeling like they were doing *'something positive'* that '*seemed to keep my MS stable'.*

35 Suicide Rate Almost Double in Patients With MS, Medscape Medical News, October 08, 2015
36 A lottery of treatment and care – MS services across the UK, MS Society (2013)
37 MS Society's 'Perspectives of people with MS on relapses and disease modifying drugs' 2010, Appendix B

Helping people with MS to remain in work

In an MS Society survey we found that, at some point, a relapse had prevented 82 per cent of pwMS from carrying out their work duties (paid employment) and that a further 89 per cent were unable to fulfil their usual roles and responsibilities during a relapse. Over half of the respondents reported that a relapse often or always has an impact on their ability to carry out their work duties.[38]

Reducing relapses for many pwMS, these DMTs have helped people stay in work without having to take time off.

Case study:

'*It absolutely changed my life! I was able to remain relatively well for five years whilst on Rebif. I carried on working as normal and had no relapses in all the time I was on treatment'.* Another person commented on Copaxone: '*I don't think that others (DMTs) would have allowed me to live as independently as I have with my home life and work'.*

Positive impact on carers

PwMS often rely on support from family and/or friends to help them to manage the impact of having MS, to help them remain independent and lead a fuller life. This includes support with everyday tasks like washing and dressing and getting out and about. At times of relapses and as disability progresses the need for this support increases and the impact on carers can be greater. Our 2012 survey on the needs of pwMs found that out of the 10,530 pwMS who responded 71 per cent received care, support or assistance from a friend or family member. [39] The effect MS has not only on the person's life who has the condition but also on those close to them is significant. The treatments in this appraisal have been shown to reduce the relapse and disability rate of pwMS and therefore reduce the impact on carers and most likely reduce the cost of management associated with MS.

Please explain any advantages described by patients or carers for the treatment(s) being appraised compared with other NHS treatments in England.

MS Society research into what influences pwMS decisions on whether to take DMTs found that there is a substantial number of people who had chosen not to take DMTs because of they considered not enough was known about the risks and side effects (32%).[40] Of those who had chosen to take a DMT, 65% said that the treatment they chose had the most acceptable potential side effects. This highlights the importance of knowing that DMTs are safe and what side effects can be expected for pwMS. Beta interferons and glatiramer

[38] Ibid
[39] Right treatment, right time? How people with MS make decisions about disease modifying drugs, MS Society, 2014
[40] Ibid

acetate represent the DMTs with the least potential side effects for pwMS and are therefore an important treatment option for pwMS.

A study of American neurologist's decision making process for MS prescribing found that the most important attributes of DMT medication selection were (in order of importance) efficacy, safety, tolerability, patient preference, and convenience.[41] This study asked neurologists to report on the patient's feedback on the therapy they were taking. While there was the strongest satisfaction rate with Fingolimod, pwMS were generally considered to be satisfied with their beta interferon or glatiramer acetate treatment.

Research into the tolerance of pwMS to take risks with DMTs has found that 15-23% of respondents were not willing to take any risk for their MS therapy. This study found the factors such as gender, age, disability and information seeking behaviour influenced risk tolerance. [42] It is important that pwMS continue to be able to access beta interferons and glatiramer acetate as they represent treatment choices where there is a known safety record.

The safety record was a deciding factor for many of the people who fed into the MS Society's case studies. One person reported choosing Copaxone for its safety record and lower risk of side effects. While another chose Copaxone as they were trying to get pregnant. Another person described how they had been on Tecfidera but it had made them '*very unwell*' so had switched to Copaxone where the side effects experienced had been minimal. Another person commented on Copaxone's lack of side effects being the main appeal despite their personal preference not to use injections: '*Bit annoying having to inject every day but I'd rather that than the yucky side effects of some of the others*.' While another person commented that '*The side effects on many of the tablet treatments were quite scary having just been diagnosed. Avonex seemed like the easy option with just having the one, quick injection a week.'*

The reasons for taking one treatment over another were diverse. Of the beta interferons and glatiramer acetate currently available on the NHS, people tend to choose an option they feel is right for them depending on factors including delivery method and side effects. A number of people spoke of being drawn to Avonex because it was administered once weekly, others stated they chose Copaxone because the daily injections made it easier for them to remember. Others preferred options such as Rebif as they found intra muscular injections too painful.

Other people commented on the '*straight forward pen device*' which Copaxone, Betaferon, Rebif and Avonex are now self-administered with, making these options the most attractive choices. These developments in how the DMTs are administered show that improvements are being made to reduce the side effects and ease of use.

[41] Hanson et al, Treatment selection and experience in multiple sclerosis: survey of neurologists, Patient Prefer Adherence.;8:415-22, April 2014

[42] Fox et al, Risk tolerance to MS therapies: survey results from the NARCOMS registry, Mult Scler Relat Disord. 4(3):241-9, May 2015

Diversity of choice in treatments offered by the NHS means that pwMS are more likely to find the DMT which best suits their condition and lifestyle. This contributes to the overall cost effectiveness of MS on the NHS and wider support services as more people on DMTs results in less relapses and slower disease progression.

If you know of any differences in opinion between patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

One case study, reported disagreeing with their parent over their treatment option. While their parent felt that, as the DMT stopped their relapses, it was worthwhile tolerating any potential side effects. This particular person felt that this DMT was not the right treatment for them due to the side effects they experienced. Though only one such incidence such as this was raised in the call for evidence, it does underline the need for pwMS to be at the centre of the decision making process when it comes to how their MS is treated.

5. What do patients and/or carers consider to be the disadvantages of the treatment(s) being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Despite clear evidence that early treatment is the most effective way of slowing the progression of MS, the UK has one of the lowest prescribing rates in Europe. The MS Society has and continues to carryout research into identifying the key barriers to more pwMS taking DMTs. Many, who fed into the case studies for this submission, describe feeling like they were not given enough of an option about which DMT they should take, while others feel the

potential side effects carry too great a risk.[43] All pwMS should be given access to a MS health professional on an annual basis in order to review their treatment and their disease progression and be given the opportunity for a shared decision making role with their clinician on what DMT to take. MS affects people differently and different treatments may be more appropriate depending on disease activity.

Please list any concerns patients or carers have about the treatment(s) being appraised.

The long history of use of these DMTs means that the range of side effects that each carry are well catalogued. The most common are injection related bruising and skin conditions, flu like symptoms immediately after injecting, and headaches and migraines.

These side effects can have a negative impact on the lifestyle of pwMS. Discomfort and frequent sickness means they are less able to lead a full life as they might be if they were side effect free. A negative mental health impact can be experienced from the sickness experienced, and marks left from skin reactions can affect people's confidence. A number of people also report developing needle phobia from the regular injecting and needing to rely on their partner's assistance.

The storage needs of the DMTs and the frequency of administering can also have a negative impact on some people's travel plans, making them more reluctant to go abroad, when they are not sure whether they will have access to a fridge.

Another negative mental health impact mentioned by some people taking these DMTs was that frequent injections served as a constant reminder of having MS; '*remembering to inject in the evening made me remember I am ill and kept the disease at the front of my mind.*'

The side effects vary somewhat depending on which of the treatments are being taken, with the below being most identified for each:

Beta Interferons

- Flu like symptoms such a headaches, fatigue, muscle ache, fever
- Injection site reactions including pain, swelling and redness
- Can be painful to inject
- Potential liver damage

Glatiramer Acetate

- Injection site reactions including bruising and swelling
- Weight gain

[43] Right treatment, right time? How people with MS make decisions about disease modifying drugs, MS Society, 2014

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

6. Patient population

Are there any groups of patients who might benefit more from the treatment(s) than others? If so, please describe them and explain why.

As access rates to DMTs in the UK are so low, it is important that the needs and concerns of pwMS are covered by the treatment options available. These DMTs provide pwMS who are particularly concerned about the side effects of higher efficacy DMTs an option with a known safety record. They also provide PwMS who have more 'quiescent' MS DMTs that are better suited to their MS, as recommended by the ABN guidelines.

These DMTs are the only first line treatments which are recommended to be taken until conception, with the option to continue while pregnant.[44] This represents a significant option to slow disease progression while allowing people to start a family.

The evidence shows that earlier treatment can greatly improve long term outcomes compared to starting treatment later. This is also the case for people diagnosed with CIS as studies have shown a reduction in CDMS for those on early treatment.

Are there any groups of patients who might benefit less from the treatment(s) than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment(s)?

X Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment(s) as part of their routine NHS care reflects the experiences of patients in the clinical trials.

[44] Vukusic et al, Multiple Sclerosis and pregnancy, Revue Neurologique, Volume 162, Issue 3, Pages 299–309, March 2006

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

Due to the length that clinical trials have tended to operate in their focus is often on relapse rates rather than disability progression which is much harder to capture. The observational data achieved through the RSS is thus an integral source of evidence for assessing the cost effectiveness and long term benefits of these DMTs.

If already available in the NHS, are there any side effects associated with treatment(s) being appraised that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

X Yes ☐ No

If yes, please provide references to the relevant studies.

The UK patient experience of relapse in MS treated with first disease modifying therapies
Duddy M, et al.
Multiple Sclerosis and Related Disorders , Volume 3 , Issue 4 , 450- 456 http://www.msard-journal.com/article/S2211-0348(14)00014-5/abstract

Patient Preferences In The Choice Of Disease Modifying Drugs For Multiple Sclerosis
Bergmann A, et al.
Neurology 2014;82(10): Supplement P3.137
http://www.neurology.org/content/82/10_Supplement/P3.137

Treatment selection and experience in multiple sclerosis: survey of neurologists
Hanson KA, et al.
Patient Prefer Adherence. 2014; 8: 415–422.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3979792/

A discrete choice experiment to determine patient preferences for injection devices in multiple sclerosis.
Shingler SL, et al.
J Med Econ. 2013 Aug;16(8):1036-42.
http://www.ncbi.nlm.nih.gov/pubmed/23730944

Preferred features of oral treatments and predictors of non-adherence: two web-based choice experiments in multiple sclerosis patients.
Wicks P, et al.
Interact J Med Res. 2015 Mar 5;4(1):e6

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4376178/

A discrete-choice experiment to determine patient preferences for injectable multiple sclerosis treatments in Germany.
Poulos C, et al.
Ther Adv Neurol Disord. 2016 Mar;9(2):95-104
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4784251/

Patient Preferences for Injectable Treatments for Multiple Sclerosis in the United States: A Discrete-Choice Experiment.
Poulos C, et al.
Patient. 2016 Apr;9(2):171-80
http://www.ncbi.nlm.nih.gov/pubmed/26259849

Patient preferences for disease-modifying drugs in multiple sclerosis therapy: a choice-based conjoint analysis
Utz KS, et al.
Ther Adv Neurol Disord. 2014 Nov;7(6):263-75.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4218877/

Multiple sclerosis patients' benefit-risk preferences: serious adverse event risks versus treatment efficacy.
Johnson FR, et al.
J Neurol. 2009 Apr;256(4):554-62.
http://www.ncbi.nlm.nih.gov/pubmed/19444531/

Patient preferences for attributes of multiple sclerosis disease-modifying therapies: development and results of a ratings-based conjoint analysis.
Wilson LS, et al.
Int J MS Care. 2015 Mar-Apr;17(2):74-82.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4399770/

Risk tolerance to MS therapies: Survey results from the NARCOMS registry.
Fox RJ, et al.
Mult Scler Relat Disord. 2015 May;4(3):241-9.
http://www.ncbi.nlm.nih.gov/pubmed/26008941

There are also the papers by Heesen, Kopke, Kasper et al on shared decision making, for example:

Decisions on multiple sclerosis immunotherapy: new treatment complexities urge patient engagement.
Heesen C, et al.
J Neurol Sci. 2011 Jul 15;306(1-2):192-7.
http://www.ncbi.nlm.nih.gov/pubmed/20920815

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

If these treatments were no longer on the NHS, pwMS who are inclined to take a low risk option but are unable to swallow would be left with no suitable DMT as the only other equivalent low risk DMT option is the oral treatment teriflunomide.

Are there groups of patients who would have difficulties using the treatment(s) being appraised or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

9. Other issues

Do you consider the treatment(s) being appraised to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- These DMTs have been proven to have a moderate efficacy rate in slowing disability progression and relapse rates for pwMS.
- These DMTs offer pwMS a choice between lower risk, moderately effective or higher risk, higher efficacy treatments. It is important that this choice should be patient orientated and led.
- MS affects people differently and people react to the available DMTs differently. The more options available the greater chance that people find the treatment which works for them.
- These DMTs have a long and proven safety record, providing an option for people who are concerned of the greater risk of newer treatments.
- The DMTs enable pwMS to stay in work and off benefits longer, meaning savings are made in the NHS, social care and the disability budget and people can live more independent lives.

Appendix A: Table of Clinical Trials

Interferon Beta 1a – Subcutaneous	*Findings of Trial*
AUSTIMS Research Group. J Neurol Neurosurg Psychiatry 1989;52:566-574 http://jnnp.bmj.com/content/52/5/566.full.pdf	No significant change in disability progression between control and placebo groups Side effects unspecified (no new ones witnessed compared to previous trials)
PRISMS Trial. Ann Neurol 1999;46:197-206.	These results provide strong, objective evidence to support the positive clinical results of reduction in relapses and delay in disease progression. In addition, they also demonstrate a significant dosage effect, favoring the 44-µg dose
SPECTRIMS Study. Neurology 2001;56:1496-1504. http://www.ncbi.nlm.nih.gov/pubmed/11402106	Treatment with interferon beta-1a did not significantly affect disability progression in this cohort, although significant treatment benefit was observed on exacerbation-related outcomes (relapses). Exploratory post hoc analyses suggested greater benefit in women and in patients who had reported at least one relapse in the 2 years before the study.
INCOMIN Study Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). Lancet 2002;359:1453–60.	High-dose interferon beta-1b administered every other day is more effective than interferon beta-1a given once a week
A randomized study of two interferon-beta treatments in relapsing-remitting multiple sclerosis. (And IFN 1b) Neurology 2006;66(7):1056–60.	In this study, 250 microg interferon-beta-1b administered every other day did not prove clinically superior to once-a-week administration of 22 microg interferon-beta-1a.
Comparison of interferon beta products and azathioprine in the treatment of relapsing-remitting multiple sclerosis. Journal of Neurology 2007;254(12):1723–8.	The mean number of relapse during one year of the study was lower in the AZA group than in the IFNbeta products group (0.28 vs. 0.64, P < 0.05). After 12 months, 57.4% of patients receiving IFNbeta products remained relapse free compared with 76.6% of those given AZA. The Expanded Disability Status Scale (EDSS) decreased by 0.30 units in IFNbeta-treated patients (P < 0.05) and 0.46 in AZAtreated patients (P < 0.001). Treatment with IFNbeta products and AZA significantly reduces the relapse rate and EDSS score in patients with RRMS, while AZA is more effective than the IFNbeta formulations
REGARD Study. Lancet Neurol 2008;7:903-914. (comparing	There was no significant difference between interferon beta-1a and glatiramer acetate in

with GA) http://www.ncbi.nlm.nih.gov/pubmed/18789766	the primary outcome. The ability to predict clinical superiority on the basis of results from previous studies might be limited by a trial population with low disease activity, which is an important consideration for ongoing and future trials in patients with RRMS.
CAMMS223 Study Alemtuzumab vs. Interferon Beta-1a in Early Multiple Sclerosis New England Journal of Medicine 2008;359(17):1786–801.	In patients with early, relapsing–remitting multiple sclerosis, alemtuzumab was more effective than interferon beta-1a but was associated with autoimmunity, most seriously manifesting as immune thrombocytopenic purpura.
NORMIMS Study Lancet Neurol 2009;8:519-529. http://www.thelancet.com/journals/laneur/article/PIIS1474-4422(09)70085-7/abstract	Oral methylprednisolone given in pulses every 4 weeks as an add-on therapy to subcutaneous interferon beta-1a in patients with relapsing-remitting multiple sclerosis leads to a significant reduction in relapse rate. However, because of the small number of patients and the high dropout rate, these findings need to be corroborated in larger cohorts.
REFLEX Study Lancet Neurol 2012;11:33-41.	Both regimens of subcutaneous interferon beta-1a delayed clinical relapses and subclinical disease activity. The potential differences between the regimens warrant longer-term study.
CARE-MS I Alemtuzumab versus interferon beta The Lancet , Volume 380 , Issue 9856 , 1819 – 1828 2012 http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(12)61769-3.pdf	Alemtuzumab's consistent safety profile and benefit in terms of reductions of relapse support its use for patients with previously untreated relapsing-remitting multiple sclerosis; however, benefit in terms of disability endpoints noted in previous trials was not observed here. Interferon performed better than in previous trials, adding evidence to early treatment.
ADVANCE Study The Lancet Neurology , Volume 13 , Issue 7 , 657 – 665, 2014	After 48 weeks, peginterferon beta-1a significantly reduced relapse rate compared with placebo. The drug might be an effective treatment for relapsing-remitting multiple sclerosis with less frequent administration than available treatments.
Interferon Beta 1a – IM	
CHAMPS Trial Ann Neurol 2002;51:481-490.	The objective of this work was to assess the effect of interferon beta-1a (Avonex) on the rate of development of clinically definite multiple sclerosis and brain magnetic resonance imaging changes in subgroups based on type of presenting event, baseline brain magnetic resonance imaging parameters, and demographic factors in the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study

	(CHAMPS) trial. A beneficial effect of treatment was noted in all subgroups evaluated
MS: the EVIDENCE trial. Neurology 2002;59:1496-1506. (And SC)	IFNbeta-1a 44 micro g subcutaneously tiw was more effective than IFNbeta-1a 30 micro g IM qw on all primary and secondary outcomes investigated after 24 and 48 weeks of treatment
PPMS Study Neurology 2003;60:44-51.	This study has demonstrated that interferon beta-1a 30 microg was well tolerated, identified useful outcome measures, but showed no efficacy on the primary outcome measure or on most of the secondary outcome measures
EVIDENCE Study Evidence of Interferon Dose-Response-European North American Comparative Efficacy (EVIDENCE) study: a multicenter, randomized, assessor-blinded comparison of low-dose weekly versus high-dose, high-frequency interferon beta-1a for relapsing multiple sclerosis. Clinical Therapeutics 2007; 29(9):2031–48.	The comparative phase of the EVIDENCE study found that treatment of MS with SC IFN-beta1a 44 microg TIW was associated with a significant reduction in clinical and imaging measures of disease activity over 1 to 2 years, when compared with IM IFN-betala 30 microg QW treatment. The crossover phase found that patients who changed from low-dose QW treatment to high-dose TIW treatment experienced enhanced benefits of treatment without a substantial increase in adverse events
Avonex combination trial (ACT) in relapsing-remitting MS. Neurology 2009;72:535-541. http://www.empireneuro.org/sitebuildercontent/sitebuilderfiles/ACT2009.pdf	This trial did not demonstrate benefit of adding low-dose oral methotrexate or every other month IV methylprednisolone to interferon beta-1a in relapsing-remitting multiple sclerosis.
TRANSFORMS Study New England Journal of Medicine 2010;362(5):402–15.	This trial showed the superior efficacy of oral fingolimod with respect to relapse rates and MRI outcomes in patients with multiple sclerosis, as compared with intramuscular interferon beta-1a. Longer studies are needed to assess the safety and efficacy of treatment beyond 1 year.
TENERE Study Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial Multiple Sclerosis (Houndmills, Basingstoke, England) 2014; 20(6):705–16.	There was no difference between teriflunomide 14 mg and IFNβ-1a on ARR, though ARR was higher with teriflunomide 7 mg. The teriflunomide safety profile was consistent with previous studies.
The CombiRx trial Neurology 2012;78:PL02.003. Abstract. (comparing with GA) http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3631288/	Combining the two most commonly prescribed therapies for MS did not produce a significant clinical benefit over three years. An effect was seen on some MRI metrics. In a test of comparative efficacy, GA was superior to IFN in reducing the risk of exacerbation. The extension phase for

	CombiRx will address if the observed differences in MRI and DAFS findings predict later clinical differences.
CHAMPIONS Study Disease-Related Determinants of Quality of Life 10 Years After Clinically Isolated Syndrome. International Journal of MS Care. 2015;17(1):26-34. doi:10.7224/1537-2073.2013-041. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4338640/	These results support the development of therapies for patients with CIS that significantly reduce the risk of conversion to CDMS and the progression of physical disability to milestones as low as EDSS scores of 2.0.
Interferon Beta 1b - SC	
Multicentre double-blind study of effect of intrathecally administered natural human fibroblast interferon on exacerbations of multiple sclerosis. Lancet 1986;2:1411-1413.	In this randomised, double-blind, placebo-controlled, 2-year multicentre study intrathecally administered natural human fibroblast interferon (IFN-B) was effective in reducing exacerbations of multiple sclerosis (MS) in patients with exacerbating/remitting disease. The mean reduction in exacerbation rate of 34 patients who received IFN-B (recipients) was significantly greater during the study than that of 35 patients who received placebo (p less than 0.04)
UBC Interferon Beta and Glatiramer Acetate Therapy 15 MS/MRI study group and the IFNB multiple sclerosis study group. Neurology 1993;43:662-667.	The MRI results support the clinical results in showing a significant reduction in disease activity as measured by numbers of active scans (median 80% reduction,p = 0.0082) and appearance of new lesions. In addition, there was an equally significant reduction in MRI-detected burden of disease in the treatment as compared with placebo groups (mean group difference of 23%, p = 0.001). These results demonstrate that IFNB has made a significant impact on the natural history of MS in these patients.
The IFNB Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. Neurology 1995;45:1277-1285.	These results support but do not establish an effect of IFNB in limiting progression of disability. This study was not originally powered to demonstrate a treatment effect on disease progression. At these levels of disability, more patients or longer follow-up, or both, would be required. Accordingly, additional clinical trials will be necessary to evaluate the role of IFNB in preventing disability.
European Study Group on interferon beta-1b in secondary progressive MS. Lancet 1998;352:1491-1497.	Treatment with interferon beta-1b delays sustained neurological deterioration in patients with SP-MS. Interferon beta-1b is the first treatment to show a therapeutic effect in patients with SP-MS
BECOME Study	Patients with relapsing multiple sclerosis

Efficacy of treatment of MS with IFNbeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study Neurology 2009;72(23):1976–83.	randomized to interferon beta 1b or glatiramer acetate showed similar MRI and clinical activity.
BENEFIT Trial The Lancet Neurology , Volume 8 , Issue 11 , 987 – 997 2009 http://www.thelancet.com/journals/laneur/article/PIIS1474-4422(09)70237-6/abstract	Effects on the rate of conversion to CDMS and the favourable long-term safety and tolerability profile support early initiation of treatment with interferon beta-1b, although a delay in treatment by up to 2 years did not affect long-term disability outcomes.
BEYOND Study 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. Lancet Neurology 2009;8(10):889–97.	500 microg interferon beta-1b was not more effective than the standard 250 microg dose, and both doses had similar clinical effects to glatiramer acetate. Although interferon beta-1b and glatiramer acetate had different adverse event profiles, the overall tolerability to both drugs was similar.
Analysis of clinical outcomes according to original treatment groups 16 years after the pivotal IFNB-1b trial. J Neurol Neurosurg Psychiatry 2010;81:907-912. http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.630.9848&rep=rep1&type=pdf	The original treatment assignment could not be shown to influence standard assessments of long term efficacy. On-study behaviour of patients was influenced by factors that could not be controlled with the sacrifice of randomisation and blinding. Mortality was higher in patients originally assigned to placebo than those who had received IFNB-1b 50 mg or 250 mg. The dataset provides important resources to explore early predictors of long-term outcome
Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFNbeta-1b trial. Neurology 2012;78:1315-1322. http://research.mblwhoilibrary.org/works/43581	There was a significant survival advantage in this cohort of patients receiving early IFNβ-1b treatment at either dose compared with placebo. Near-complete ascertainment, together with confirmatory findings from both active treatment groups, strengthens the evidence for an IFNβ-1b benefit on all-cause mortality
Interferon Beta-1b for the Treatment of Primary Progressive Multiple Sclerosis: Five-Year Clinical Trial Follow-up. Arch Neurol. 2011;68(11):1421-1427. doi:10.1001/archneurol.2011.241. http://archneur.jamanetwork.com/article.aspx?articleid=1107912	Modest but beneficial effects of interferon beta-1b on clinical variables and brain atrophy development were observed 5 years after trial termination. Moreover, in-trial lesion activity correlated with EDSS progression after trial termination. Therefore, we provide evidence to consider immunomodulation as a sensible approach to treat primary progressive multiple sclerosis
Glatiramer Acetate	
Bornstein RRMS Study N Engl J Med 1987;317:408-414.	These results suggest that Cop 1 may be beneficial in patients with the exacerbating-remitting form of multiple sclerosis, but we emphasize that the study is a preliminary one and our data require confirmation by a

	more extensive clinical trial.
Bornstein SPMS Study Neurology 1991;41:533-539.	We found a significant difference at 24 months between placebo and Cop 1 at one but not the other center. Two-year progression rates for two secondary end points, unconfirmed progression, and progression of 0.5 EDSS units, (p = 0.03) are significant.
The copolymer 1 multiple sclerosis study group. Neurology 1995;45:1268-1276.	The primary end point was a difference in the MS relapse rate. The final 2-year relapse rate was 1.19 +/- 0.13 for patients receiving copolymer 1 and 1.68 +/- 0.13 for those receiving placebo, a 29% reduction in favor of copolymer 1 (p = 0.007) (annualized rates = 0.59 for copolymer 1 and 0.84 for placebo).
Comi 2001 European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. Annals of Neurology 2001;49(3):290–7. [PUBMED: 11261502]	Treatment with GA showed a significant reduction in the total number of enhancing lesions compared with placebo (-10.8, 95% confidence interval -18.0 to -3.7; p = 0.003).
Glatiramer acetate in primary progressive multiple sclerosis: results of a Interferon Beta and Glatiramer Acetate Therapy 17 multinational, multicenter, double-blind, placebo-controlled trial. Ann Neurol 2007;61:14-24. (and IFN B) http://onlinelibrary.wiley.com/doi/10.1002/ana.21079/epdf	The trial failed to demonstrate a treatment effect of GA on primary progressive multiple sclerosis. Both the unanticipated low event rate and premature discontinuation of study medication decreased the power to detect a treatment effect. Post hoc analysis suggests GA may have slowed clinical progression in male patients who showed more rapid progression when untreated The trial failed to demonstrate a treatment effect of GA on primary progressive multiple sclerosis. Both the unanticipated low event rate and premature discontinuation of study medication decreased the power to detect a treatment effect. Post hoc analysis suggests GA may have slowed clinical progression in male patients who showed more rapid progression when untreated The trial failed to demonstrate a treatment effect of GA on primary progressive multiple sclerosis. Both the unanticipated low event rate and premature discontinuation of study medication decreased the power to detect a

	treatment effect. Post hoc analysis suggests GA may have slowed clinical progression in male patients who showed more rapid progression when untreated.
A multicentre, multinational extension of the European/Canadian double-blind, placebo-controlled, MRI-monitored trial Mult Scler. 2007; 13(4): 502-8 http://www.ncbi.nlm.nih.gov/pubmed/17483532	A six year study of patients taking glatiramer acetate concluded that early use of the treatment has a bearing on efficacy, with those taking treatment (rather than placebo) from the outset being less likely to be using a walking aid at six years
PROMiSe Trial Study Group. J Neurol Sci 2009;286:92-98.	The analyses conducted do not support a treatment by gender interaction for GA in either PPMS or relapsing forms of MS. Nor could we find consistent precedence in the literature for important effects of gender on outcome, recognizing that such effects have not always been carefully sought. It remains reasonable to consider that there exist differences in the rates of clinical disease progression between men and women with MS that should be better studied.
PreCISe study The Lancet (British edition) 2009;374:1503-1511. (40 vs 20mgs) http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(09)61259-9.pdf	Early treatment with glatiramer acetate is efficacious in delaying conversion to clinically definite multiple sclerosis in patients presenting with clinically isolated syndrome and brain lesions detected by MRI
FORTE Study Phase III dose-comparison study of glatiramer acetate for multiple sclerosis Annals of Neurology 2011;69(1):75–82	In relapsing-remitting MS patients, both the currently-approved GA 20 mg and 40 mg doses were safe and well-tolerated, with no gain in efficacy for the higher dose.
CONFIRM Study Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. New England Journal of Medicine 2012;367(12):1087–97.	In patients with relapsing-remitting multiple sclerosis, BG-12 (at both doses) and glatiramer acetate significantly reduced relapse rates and improved neuroradiologic outcomes relative to placebo. (Funded by Biogen Idec; CONFIRM ClinicalTrials.gov number,
GALA Study Three times weekly glatiramer acetate in relapsing–remitting multiple sclerosis 2013 DOI: 10.1002/ana.23938 http://onlinelibrary.wiley.com/doi/10.1002/ana.23938/abstract;jsessionid=2641BB8E1DC22602287A1A233549CCDC.f03t03	GA 40mg sc tiw is a safe and effective regimen for the treatment of RRMS, providing the convenience of fewer sc injections per week. ANN NEUROL 2013;73:705–713 GA 40mg tiw was associated with a 34.0% reduction in risk of confirmed relapses compared with placebo (mean annualized relapse rate = 0.331 vs 0.505; $p < 0.0001$). Patients who received GA 40mg tiw experienced highly significant reduction ($p < 0.0001$) in the cumulative number of gadolinium-enhancing T1 (44.8%) and new or newly enlarging T2 lesions (34.7%) at months 6 and 12. GA 40mg tiw was safe and well tolerated

Equivalence of Generic Glatiramer Acetate in Multiple Sclerosis: A Randomized Clinical Trial. JAMA Neurol. 2015;72(12):1433-1441. doi:10.1001/jamaneurol.2015.2154. http://archneur.jamanetwork.com/article.aspx?articleid=2451333	As treatment for relapsing-remitting multiple sclerosis, glatiramer acetate generic drug and brand drug had equivalent efficacy, safety, and tolerability. The primary goal of the study was to compare the number of active MS lesions on MRI brain scans in those who were given GTR, Copaxone, or placebo during months 7, 8, and 9. The results show that this MRI measure of disease activity was significantly reduced in both the Synthon GTR and the Copaxone groups when compared with the placebo group within a range that indicates equivalence. Reported adverse reactions were similar between the GTR and Copaxone groups and in line with injection site reactions and others known to be associated with Copaxone.
GLACIER Study Multiple Sclerosis and Related Disorders , Volume 4 , Issue 4 , 370 – 376 2015 http://www.msard-journal.com/article/S2211-0348(15)00076-0/abstract	The efficacy and safety of glatiramer acetate (GA) 20 mg/mL once-daily subcutaneous injections (GA20) in relapsing-remitting multiple sclerosis (RRMS) is well-established. However, injection-related adverse events (IRAEs) may impede treatment adherence and tolerability. GA 40 mg/mL three-times weekly (GA40) also has a favorable efficacy and safety profile

Appendix B: A report on the perspectives of people with MS on relapses and disease modifying drugs

Perspectives of people with MS on relapses and disease modifying drugs

MS Society

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Contents

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Executive summary

This report documents the methods and results of a 2010 MS Society survey of people with multiple sclerosis (MS) who have or have had relapsing-remitting MS. The purpose of the survey was to capture the experiences and feelings of people with MS in relation to relapses and disease modifying drugs (DMDs). The survey had three main sections with the first asking about experiences of relapses in general, second asking about experiences of DMDs that can be self-administered by weekly injections and the third section asking about experiences of Tysabri, a disease modifying drug that is administered monthly as an infusion in a clinic. In addition to multiple choice questions, the survey contained some free comment sections.

Relapses have repercussions that go beyond the physical symptoms – they hinder people's ability to work and carry out their day-to-day responsibilities, limit their independence and increase reliance on other people. Respondents were also worried about how a relapse would impact on those around them. Finally, relapses not only have a serious impact on the practical organisation of one's life but also on an emotional level with feelings of frustration and anxiety being common.

Issues related to difficulty of use were raised with both treatments. With injected DMDs the main concerns related to the injections themselves. People found injecting to be difficult and often had to rely on other people to help them with this. Injection site reactions were not only common but often very painful too. Other side-effects also appeared common and debilitating. The frequency of the injections means that life has to be planned around the treatment to avoid socially awkward situations and to ensure injecting can be done in privacy. Overall, the treatment impacted the person injecting, those close to them, and often the person's ability to carry out their responsibilities at work and elsewhere.

Issues related to Tysabri had a slightly different emphasis. Whilst the infusion itself appeared to be tolerated better than injections, travelling to get the treatment posed problems and the person receiving the treatment was consequently more dependent on other people. The more serious side-effects, namely the viral brain infection progressive multifocal leucoencephalopathy (PML) associated with Tysabri, caused this group of respondents to be more worried about side-effects.

The final question in the survey asked for respondents' preference for administering a disease modifying drug if three options were available: an infusion administered monthly in a hospital via a drip, self-administered injection given several times a week and a pill taken daily. The overwhelming majority (95 per cent) chose the pill option, giving ease of use, convenience to everyday life and non-invasiveness as reasons for selecting this option.

The responses illustrate the practical impact relapses and using disease modifying drugs can have on a person's everyday life, giving a clear idea what respondents would like to see improved. Both forms of treatment have strengths and weaknesses, and by identifying these strengths and weaknesses the report will draw a picture of what people with MS would want from a treatment.

The responses indicate that there was a preference for a therapy that would allow people to be in charge of their own treatment and would enable them to be independent in this sense. The treatment would easily fit in a person's everyday life and normal activities and would not have debilitating side-effects. The treatment would enable the person to carry on with their normal life, to stay in paid employment and be able to care for their family and rather than being cared for.

1. Introduction

This report documents the methods and results of a 2010 MS Society survey of people with MS who have or have had relapsing-remitting MS. The purpose of the survey was to capture the experiences of people with MS in relation to relapses and disease modifying drugs (DMDs). Although information is available about relapses in general as well as the side-effects of disease modifying drugs, it was felt important to try and gain an understanding of what people themselves thought were the problems they have to face, what they go through during a relapse and what their own experiences of taking the DMD was. The survey was designed by the MS Society Research and Policy teams.

This chapter will give some background information about MS, what treatments are available and which treatments are expected to become available in the future. After this there is a brief section describing how the survey was carried out. The rest of the report will discuss the results of the survey.

1.1. What is multiple sclerosis?

MS is the most common disabling neurological condition affecting young adults. There are around 100,000 people in the UK living with MS. MS is the result of the body's own immune system attacking and damaging myelin - a protective substance surrounding nerve fibres of the central nervous system. When myelin is damaged, messages between the brain and other parts of the body are distorted or lost. Over time, in addition to myelin damage, the nerve fibres themselves also become damaged leading to an irreversible accumulation of disability.

The causes of MS are unknown, though it is widely believed to be caused by a combination of genetic and environmental factors. Several genes have been associated with increasing the risk of developing MS and it is estimated that there could be as many as 50-100 genes linked to the condition. There is also some evidence linking a number of environmental factors to MS such as viral infections and vitamin D deficiency but the relative impact of these on causing the condition is yet to be determined.

There are four main recognised types of MS:

- Relapsing-remitting MS (RRMS):	Characterised as periods of relapse (acute MS 'attacks') followed by periods of remission (complete or partial recovery). Around 85 per cent of people are diagnosed with RRMS.
- Secondary progressive MS (SPMS):	Following an initial period of RRMS, many people develop SPMS which is characterised as a gradual accumulation of disability, either with or without relapses.
- Primary progressive MS (PPMS):	Characterised as a gradual accumulation of disability from diagnosis with no distinct periods of relapse and remission. Between 5 and 15 per cent of people are diagnosed with PPMS.
- Benign MS:	Is diagnosed if the condition has not got worse over a 10 to 20 year period and is associated with little or no disability.

There are many symptoms associated with MS, which include restricted mobility, chronic fatigue, bladder and bowel problems and cognitive impairment. MS is unpredictable and affects people in very different ways, with variability in severity, in rates of progression and in type and severity of symptoms. This unpredictability results in a major impact on the quality of life of people with MS and can often lead to periods of significant disability.

What are relapses?

Immune damage to the myelin sheath is believed to cause relapses, or MS 'attacks'. Clinicians define a relapse as an episode of neurological symptoms, lasting for at least 24 hours, that happens at least 30 days after any previous episode began. In relapses, symptoms usually come on over a short period of time and often remain for a number of weeks, but sometimes months. Relapses can vary from mild to severe. At their worst, acute relapses may need hospital treatment, but many relapses are managed at home, with the support of a GP, MS specialist nurse, and other care professionals.

Due to the varied and unpredictable nature of the condition determining an 'average' relapse rate for RRMS is not straight forward and is an issue that has caused much debate amongst the clinical community. Although a true consensus is yet to be reached, the many thousands of people currently on disease modifying drugs (DMDs) indicates that it is likely that a significant proportion of people with RRMS experience 1 or more relapses per year

Current treatments

There are four classes of DMDs licensed for RRMS and none licensed for PPMS or SPMS. The DMDs licensed for RRMS include beta interferon 1a, beta interferon 1b, glatiramer acetate and natalizumab.

The beta interferons and glatiramer acetate are delivered by self-injection (under the skin or into the muscle) at frequencies ranging from once daily to once weekly. These are usually prescribed to people that have experienced two or more relapses over a two year period. The precise way these DMDs work is unclear but they appear to modulate the immune system in a way that reduces the damage caused to myelin. It has been shown that these DMDs reduce relapse rates on average by 33 per cent; there is limited evidence on their long term effect on disability progression. There are a number of side effects associated with these DMDs that have a significant impact on quality of life, including injection site reactions and flu-like symptoms.

Natalizumab is a monoclonal antibody treatment delivered by monthly infusion in a hospital clinic. It is prescribed for highly active RRMS where either the relapse rate or severity of relapses is considered high. Natalizumab works by preventing the immune system cells, that cause the damage associated with MS, from entering the central nervous system thereby preventing the damage to myelin. It has been shown that natalizumab can reduce relapse rates by around 67 per cent and can reduce the risk of disability progression by around 40 per cent. There are a number of side effects associated with natalizumab the most serious being a one in a 1000 risk of developing PML, a viral infection of the brain which can often lead to death.

73 per cent of the respondents to this survey had taken one or more of these drugs. As will be shown later in the report, this group of people have a wealth of first-hand experience of the benefits but also the down-sides of these treatments.

Treatments on the horizon

There is a huge need for better treatments for MS. There is no cure for the condition and no DMDs for non-relapsing progressive forms of MS. Although there are available treatments for RRMS their effectiveness is varied and the side effects can be significant.

There are a number of new potential treatments on the horizon that, from clinical trial data, look to be at least as good as if not potentially better than existing treatments. The first wave of potential new treatments for RRMS include the oral therapies, cladribine and fingolimod, that act on the immune system. Clinical trial data suggests that these reduce relapse rates by around 50 per cent. As with all DMDs these do have side effects, but they are available as a pill thereby eliminating the need to self-inject and therefore eliminating injection site reactions – a common side-effect of injecting.

The second wave of potential new treatments for RRMS may include more powerful monoclonal antibodies that suppress the immune system. These include alemtuzumab which, although associated with a number of side effects, appears to reduce relapse rates significantly and reduce disability progression by around 70 per cent, even reversing disability in some cases.

The next wave is difficult to predict but it is likely to include potential new treatments that will look to promote the repair of myelin or protect nerve fibres from damage rather than having an effect on the immune system. A combination of this type of treatment with a treatment that acts on the immune system may help in significantly reducing the effects of MS in the long term; however, this is the vision of future MS treatment which is not likely to become a reality for many years.

This report concentrates on the treatments that are currently available, betainterferons, glatiramer acetate and natalizumab.

1.2. How was the survey carried out?

Administration of the survey

The questionnaire was available online (at surveymonkey.com) from 26th March until 14th April 2010 and was advertised on the MS Society website and intranet. Information and a link to the questionnaire were also emailed to all MS Society area teams and to the directors of MS Society Northern Ireland, Wales and Scotland who all distributed the information as they saw fit. Information and a link to the questionnaire were also posted in MS Society's Facebook

page (with 5000 fans) and sent to 3000 Twitter followers, and included in the Campaigns eNewsletter and MS Society eNewsletter.

Inclusion and exclusion criteria

The total number of respondents was 1129. However, only those who had or had previously had relapsing-remitting MS or who had benign MS were included in the study, whereas those who did not have MS or had primary progressive MS were excluded from the survey. One of the options in the screening question was "I have MS but do not know which type", these responses were also included. Finally, surveys that were only partially filled in were also excluded. The total number of responses included in the analysis was therefore 1007.

The average/typical respondent was female (73 per cent of all respondents), was aged between 31-50 (67 per cent), and had RRMS (80 per cent). They had experience of taking at least one of the disease modifying drugs (73 per cent). For distribution of type of MS and age of the respondents, please see figures 1 and 2 below.

Figure 1

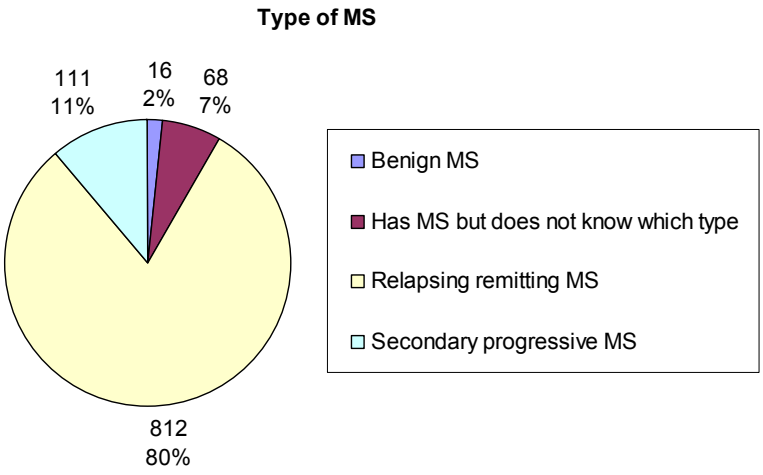
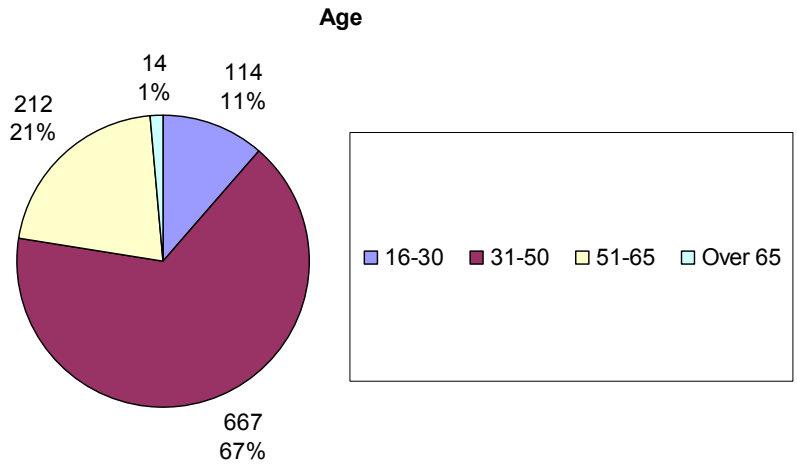


Figure 2



Analysis

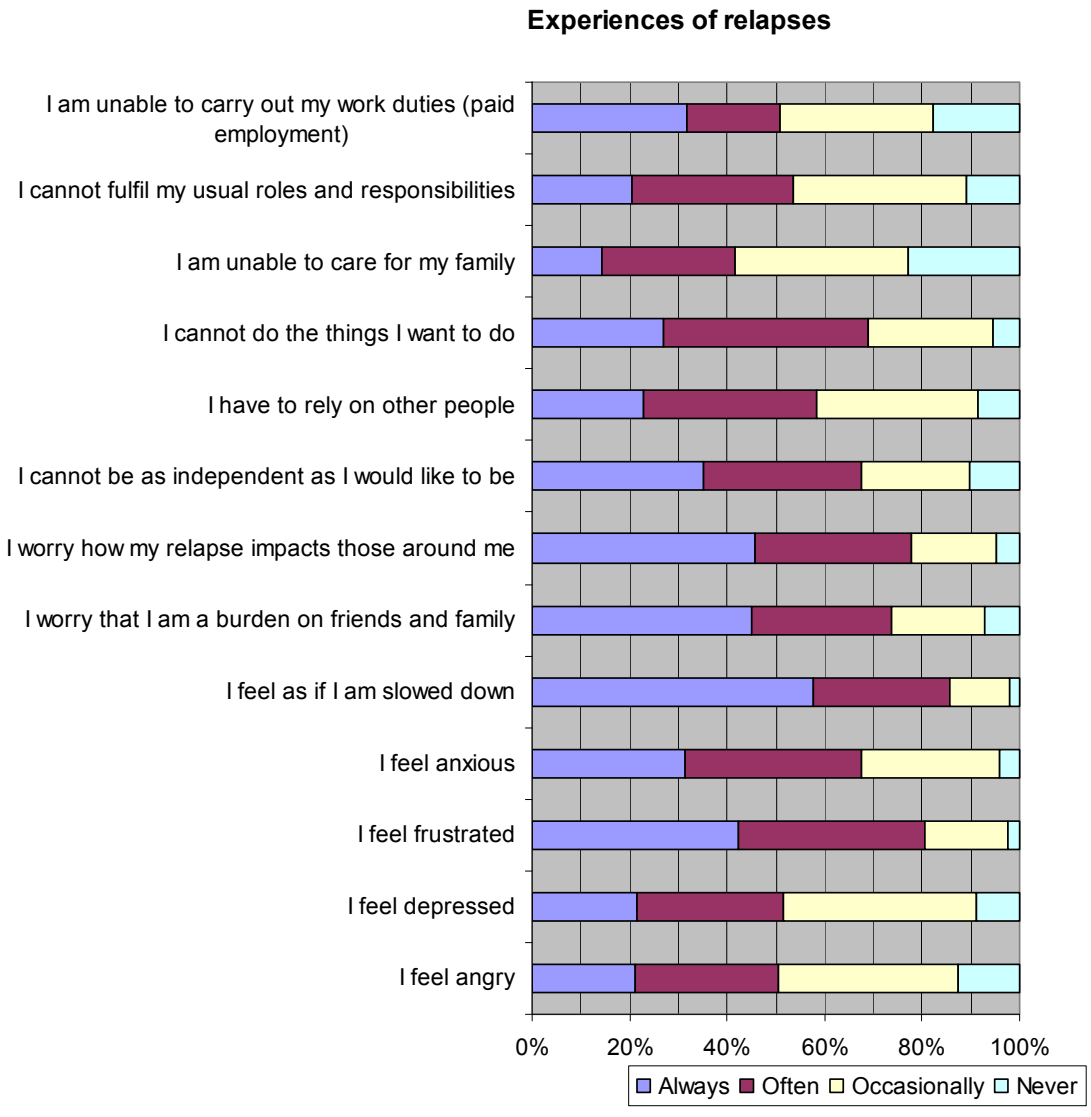
Descriptive statistics were used to analyse the results of the survey. Due to rounding, the percentages for each questions do not always add up to 100 per cent. Quotes from the free comment sections were extracted to illustrate the results of the survey, but no systematic analysis was conducted on the free text answers.

2. Experiences of relapses

All those who qualified to take part in the survey were asked about their experiences in relation to relapses. The total number of respondents for this section was 1007.

The respondents were first presented with statements related to relapses and asked to rate them according to how closely the statements reflected their own experiences. The response options were 'always', 'often', 'occasionally' and 'never'. The statements ranged from ones dealing with the practical impact of relapses on the respondents' everyday life to ones scoping emotional impact of relapses. The statements and the distribution of responses to them are presented in the table below (figure 3).

Figure 3



Work and other responsibilities

On being asked whether a relapse prevents the respondent from carrying out their work duties (particularly in reference to paid employment), the most frequent response (32 per cent) was 'always' (Figure 3). If response categories 'always' and 'often' are combined, over half of the respondents (51 per cent) reported that a relapse has an impact on their ability to carry out their work duties.

The impact of relapses on work was also reflected in the answers given in the free comment section:

> *"Relapses make sustaining full-time work so much more difficult as they make each day such an effort and I am exhausted, although I still manage to hold down a responsible job."*

> *"I had two relapses last year one straight after the other. These relapses can be very debilitating and take away your independence. I work part-time and when I have to have time off sick I feel I am letting people down. I am currently undertaking light duties as my mobility is not what it was. This upsets me greatly as I feel that due to MS I am unable to do the job I have enjoyed for many years."*

The difficulties of holding on to one's job were also visible in the responses. Adjustments are sometimes needed to enable someone with MS to stay working. This was clearly something where some respondents were more fortunate than others:

> *"I am lucky that I have an understanding employer who has agreed for me to work from home part of the week and when I am having problems (mobility wise). This I have found very useful, helping me from a fatigue point of view as well as allowing me to continue to work."*

> *"I try to limit the impact at work by taking annual leave instead of sick leave if I feel I am losing energy which means I spend a lot of annual leave in bed recovering from work."*

> *"I have had 4 bad relapses in the last 14 months causing me to have to take 6 months off work in total. I have now been made redundant and wonder if it was because of the disability?"*

18 per cent of respondents indicated they were never unable to carry out their work duties due to a relapse. It is worth noting that unemployment among people with MS is higher than in the general population, and this might go some way to explain the number of responses in category 'never'.

Finally, being unable to carry out one's responsibilities is not just restricted to employment. When asked about fulfilling one's roles and responsibilities in general, over a half of the respondents (53 per cent) thought they were 'often' or 'always' unable to fulfil their usual roles and responsibilities because of a relapse.

Independence

Some of the statements scoped respondents' perceptions of independence in relation to a relapse. Overall, the great majority (some 91 per cent) felt that they have to rely on other people at least occasionally, with nearly 60 per cent reporting they had to rely on other people either always (23 per cent) or often (35 per cent).

> *"I have had awful relapses, where I have been unable to do anything for myself for months, until relapse passes, leaving you weak, feeling dreadful and depressed."*

> *"If there was a high risk treatment which could potentially cure my MS I would seize the opportunity with both hands as I want to be normal again and not have to endure debilitating relapses several times a year, which set me back so far and mean I have rely on others to help me, when I just want to be able to do the things that everyone else takes for granted."*

> *"I have persevered with the inconvenience of injections because the relapses would be worse. The injections require a bit of planning and some symptoms on the day of injection, but I feel this is worth suffering to minimise the likelihood of another relapse, and the inevitable worry and complete dependence on family to care for me that would result."*

When presented with the statement "I cannot be as independent as I would like to be", 35 per cent of respondents felt that this reflected their experience always, with a total of 89 per cent of respondents feeling that this reflected their experience at least occasionally.

> *"I found relapses very frightening and upsetting, having to take time off work, deal with new symptoms, losing control of my life and independence and the uncertainty of not knowing what residual damage would be left when the relapse ended."*

Worry about other people

There were two statements scoping whether respondents were worried how their situation impacts those around them. It was very clear that this was a concern to many, with 46 per cent indicating they were always worried about how their relapse impacts on others and 45 per cent saying that they always worrying that they are a burden to their friends and family.

A relapse does not only affect the person with MS but also those around them.
Particularly with a reduction in independence, families are often closely involved with care but the relationship can become strained under concerns for a loved one, the carers own needs and the unknown:

> *"Relapses change your life completely - not the same person at all any more. DMD are difficult to handle at time because of the bad side effects (not each week but for me I would say 3/5 weeks are a problem to me and I have had to live my life around this which is sometimes difficult, not only for me but my family too."*

"Relapses are not only worrying, painful & distressing at the time but can take a considerable amount of time to recover from, I have been left with residual problems from every relapse. I then worry about the impact on my husband and that he has to take time off work to help me. The concern that he will not cope if I become severely affected by another relapse is a genuine worry as he gets extremely frustrated with the whole MS scenario. As a very independent person this adds it's own issues to my state of mind, as well as the fact that I cannot be there as readily for my children and colleagues."

"I am fortunate that I haven't had to take drugs as yet but I do know that relapses make me feel awful and debilitated and it is very hard to explain to you family why you feel like you do."

"It has never got any easier to inject myself or any easier to ask my husband to do it for me. Indeed it can cause friction between us because we both get anxious."

Emotional well-being

Finally, there were several statements relating to general feelings during a relapse. The feeling of being slowed down was certainly one that respondents recognised, with a majority of 58 per cent claiming this to reflected their experience always. The feeling of frustration also seemed to closely reflect the respondents' experience of a relapse, with 42 per cent saying this was the case always and a further 38 per cent saying this was the case often. Finally, feeling anxious reflected nearly 67 per cent of respondents experiences either always or often. The feelings (anxiety, frustration, depression) can stem from a number of things:

"I feel frustrated as I am very independent and I am very scared losing functionality."

"Due to the change in feeling in my legs I no longer felt safe to work in my original job role when diagnosed therefore left for an office job. This lead to an episode of anxiety and mild depression which still bothers me from time to time."

"I felt extremely nervous and frightened when first told I would need to take the drugs - I became depressed at this time as the enormity of my diagnosis hit home, that this was it for life until the drugs stopped working."

"I suffered Post-natal depression which stemmed from my absolute fear of having a relapse and not being able to look after my child. This was coupled with anxiety attacks caused by fear of not getting enough sleep, becoming run down and then having a relapse. This desperately impacted my first 8 weeks after birth, which I'll never get back."

Relapses have repercussions that go beyond the physical symptoms – they hinder people's ability to work and carry out their day-to-day responsibilities, limit their independence and increase reliance on other people. Respondents were also worried about how a relapse would impact those around them as friends and family are also affected by the uncertainty of the condition. Finally, relapses not only have a serious impact on the practical organisation of one's life but also on a person's emotional well-being.

3. Experiences of disease modifying drugs

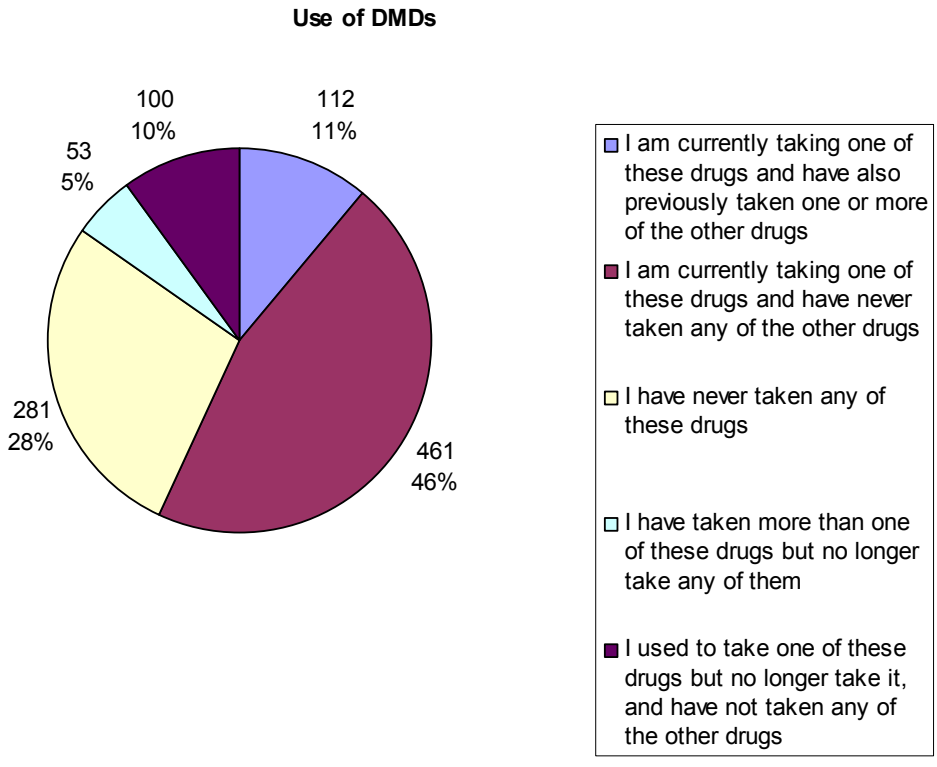
The survey also sought to find out about experiences specifically related to injecting disease modifying drugs (Avonex, Rebif, Betaferon, Extavia or Copaxone) or taking Tysabri. People who had experience of using at least one of these drugs at some point were invited to answer these sections, whereas those who had not used either at any time were excluded from this stage.

Overall, 73 per cent (N=736) of the respondents had taken at least one of these disease modifying drugs at some point in time.

3.1. Injecting disease modifying drugs

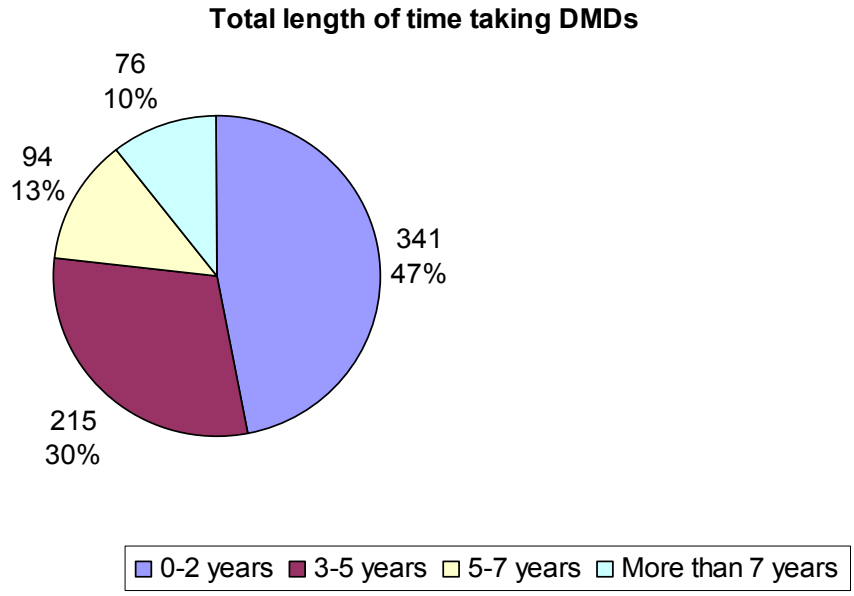
72 per cent of the respondents had taken at least one of the injected DMDs at some point in time. Of those who responded to this section, 57 per cent were currently taking one of these DMDs. 15 per cent of the respondents had tried at least one of these drugs but were no longer taking any. 26 per cent had discontinued taking one of these drugs earlier on (figure 4). Reasons for discontinuing drugs are discussed further below.

Figure 4



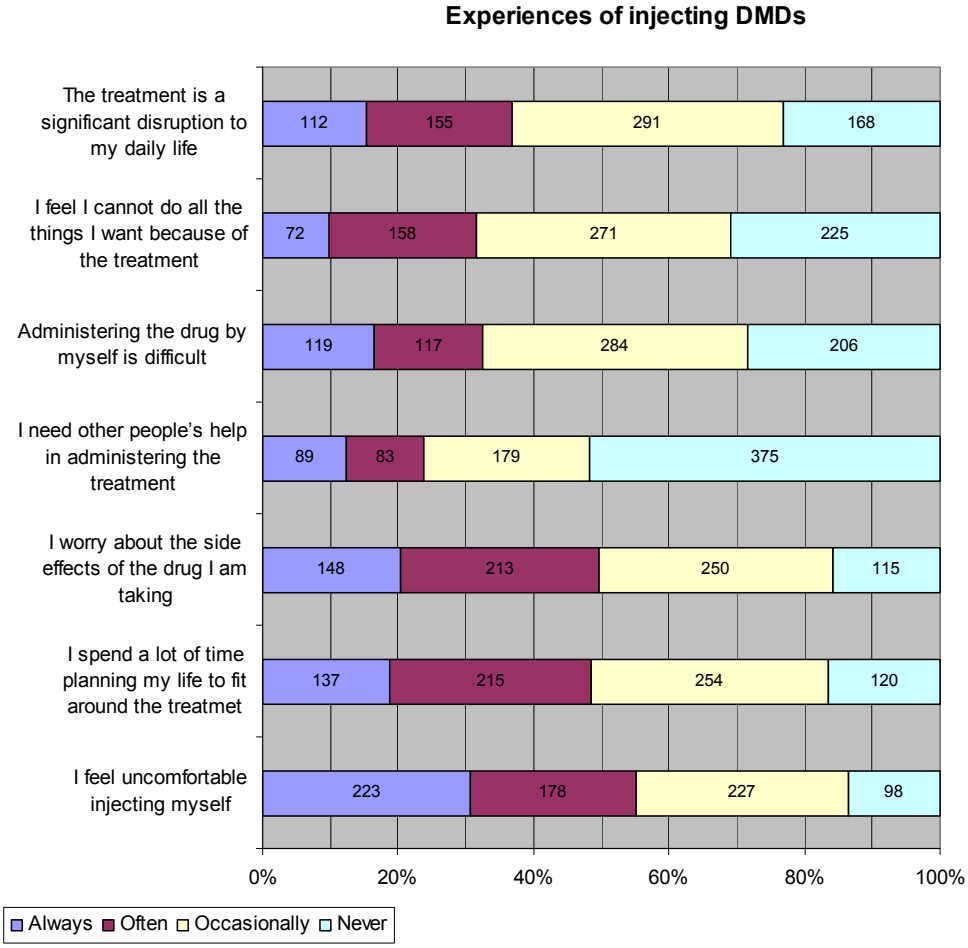
For a breakdown of the length of treatment on injected DMDs, please see figure 5.

Figure 5



Respondents were presented with statements about practicalities and experiences of injecting DMDs, and asked to rate them on a scale of Always-Never, according to how the statements reflected the respondents' experiences. Please see figure 6 below for the statements and the distribution of responses.

Figure 6



Independence

Over half of the respondents reported that they never needed other people's help in administering (mixing etc.) the drug and in a separate statement, 28 per cent found self-administration never to be difficult. Although it should not go unnoticed that there were also a significant proportion of respondents who found these areas problematic at least at times, it appears that self-administering the drug allows for more independence. This was certainly the view of some of the respondents:

> *"I would not want to go to hospital monthly for a drip – you spend enough time there or with other medical professionals. It isn't just the the time it takes for the drip, it's the recovery time too and having someone to go with you."*

> *"I feel very lucky to have the ease of use with the Rebismart and not having to be the 'patient', I can do all of my injections myself. However, my arms and legs are dotted with skin reactions, when I wear a swimming costume on holiday, I feel I need to cover up all the time. I would welcome an oral drug, so long as the side effects were similar, so that I could lead a more normal life."*

Independence enabled by self-injecting becomes even more apparent when compared with Tysabri which cannot be self-administered, and this will be discussed later in the report.

While injected DMDs may be easy to administer without other people's help, nearly 50 per cent of respondents thought they spent a lot of time planning around the treatment either always or often (figure 6). The need for planning is well illustrated by the comments describing everyday situations that are familiar to everyone, but that become problematic when you have to fit in everything that goes with the treatment:

> *"Needing to give myself an injection after a long day (e.g. after a party, night out, long journey) can be difficult. Carrying all the paraphernalia - cool box, injector, sharps box, et al - when going away can be a nuisance, frankly. Finding somewhere private to inject isn't always easy. I can't inject in some parts of my body myself, so need to rely on someone else (who isn't always around)."*

> *"It does involve planning when going on holiday as a fridge is needed in hotter climates, airlines need to be notified and delivery company contacted."*

> *"There is also the hassle of keeping the drug in the fridge (away from the children). There is all the paraphernalia with the equipment needed. Sharps box, auto injector. Having to think about taking it all on holiday. Will there be a fridge to keep the Rebif in? A place to store it at home. Being in when the delivery van comes every month."*

Although self-administered DMDs appeared to allow for more independence, they also have their problems, and need some planning to be compatible with an active life.

Injections

A little over 31 per cent of respondents felt always uncomfortable about injecting oneself. Overall, nearly 90 per cent of the respondents reported feeling uncomfortable injecting at least occasionally. The self-injection, which many respondents found difficult, featured often in the comments:

> *"It is a frightening thing being told that DMDs are only available via an injection and that you have to do it. To begin with, it controls your life as it is against human nature to hurt yourself and even trickier when trying to inject with a tremor."*

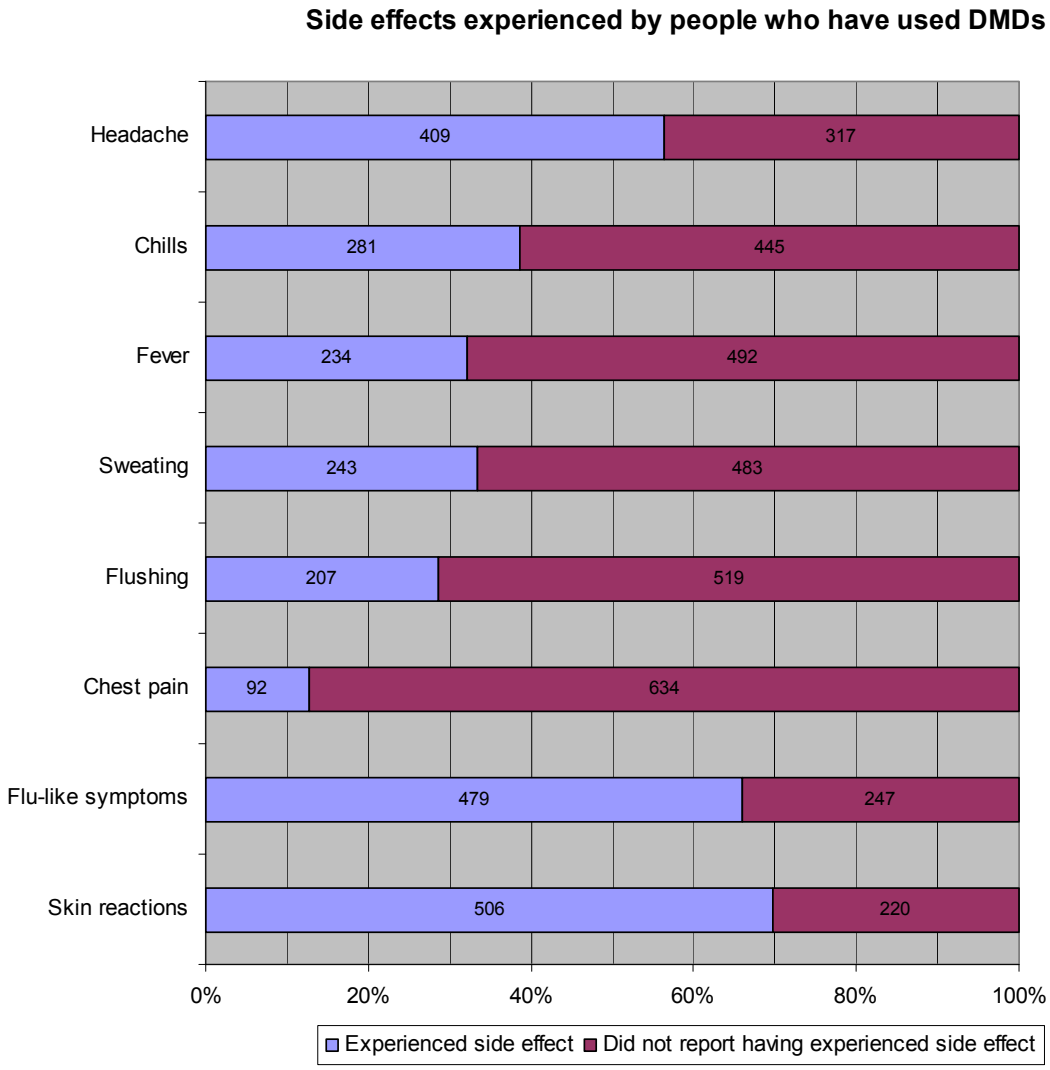
> *"Injecting daily is both painful and inconvenient. It is something that daily I dread."*

> *"It's not pleasant experiencing the flu-like symptoms, but I think this would be far easier to cope with if you didn't have to inject as well."*

Side-effects

In addition to the difficulty of injection itself, injection sites can develop painful skin reactions and this was the most commonly experienced side effect, as reported by 70 per cent of respondents (see figure 7). Other commonly experienced symptoms were flu-like symptoms (66 per cent) and headache (56 per cent). Overall, 64 per cent of the respondents had sought some form of medical advice because of the side-effects (figure 8).

Figure 7



It is not surprising then, that nearly 50 per cent of respondents said they worried about the side-effects often or always (figure 6). The impact of the side-effects was described in the free comments:

"I am a young woman and I feel this disease limits my life in ways it should not, I want to take my medication to stay well but I hate having to take injections, they hurt and make a mess of my skin."

"Sometimes the side-effects are worse than the symptoms of a relapse."

"I take a weekly injection. I don't suffer strong side effects but the following day is a bit of a write off - like a minor flu, tiredness and headaches etc and difficulties in concentrating. I can do very little on that day. To help ensure I can continue with work I inject on Friday evenings which means that I get a 1 day weekend (the Saturday being a write off). I live with this but it can be very tiring and draining - physically, mentally and emotionally."

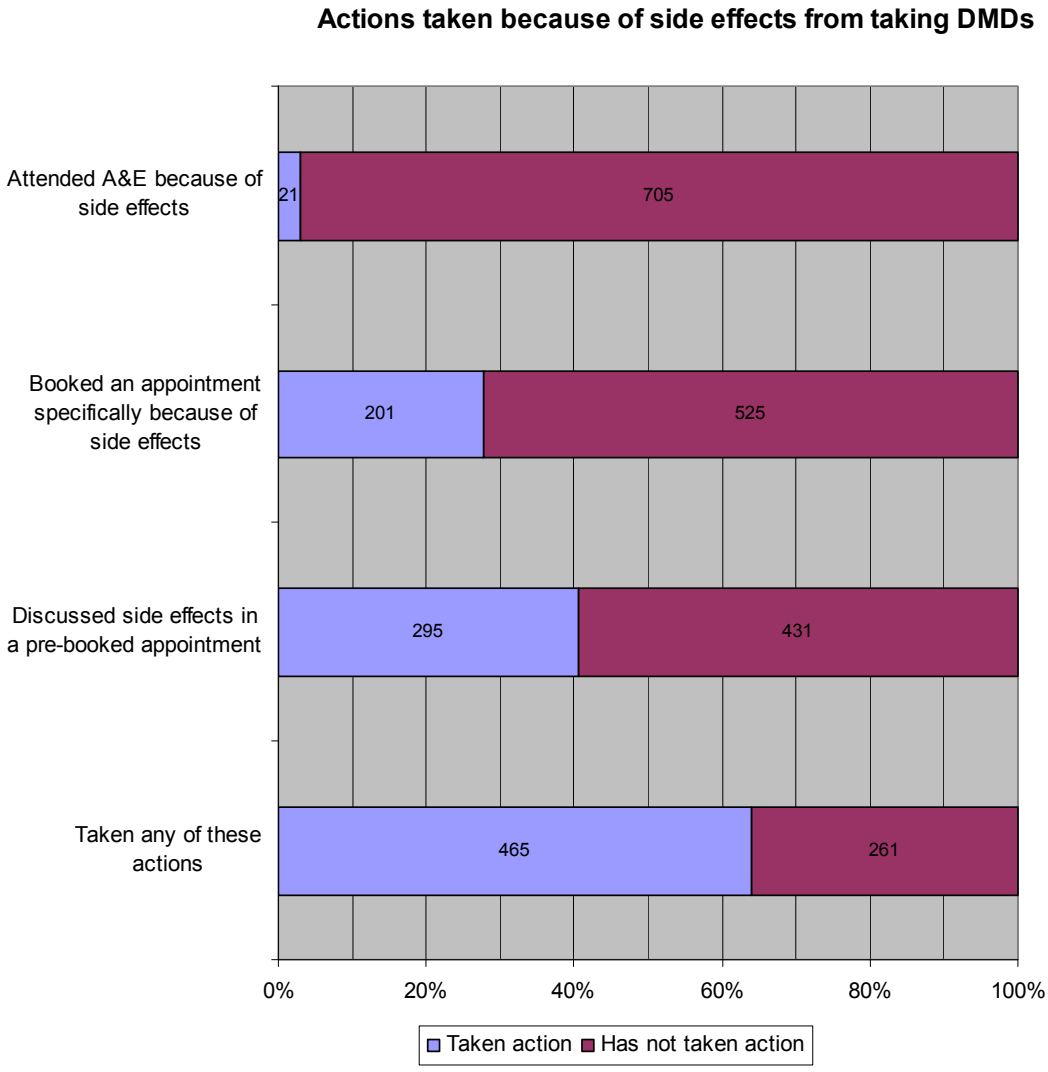
Finally, those who had discontinued one of these treatments at some point were asked for a reason for this. Common reasons were to do with the side-effects, fear of needles and ineffectiveness of treatment. Skin reactions was a side-effect that was particularly singled out and reported frequently as a reason for discontinuing a treatment.

"I found the self injection too stressful. I could not come to terms with it having a deep fear of needles."

"I couldn't inject myself. It was taking over everything else in my life!!"

"I hated the needle, the bruises and needle marks and the side effects."

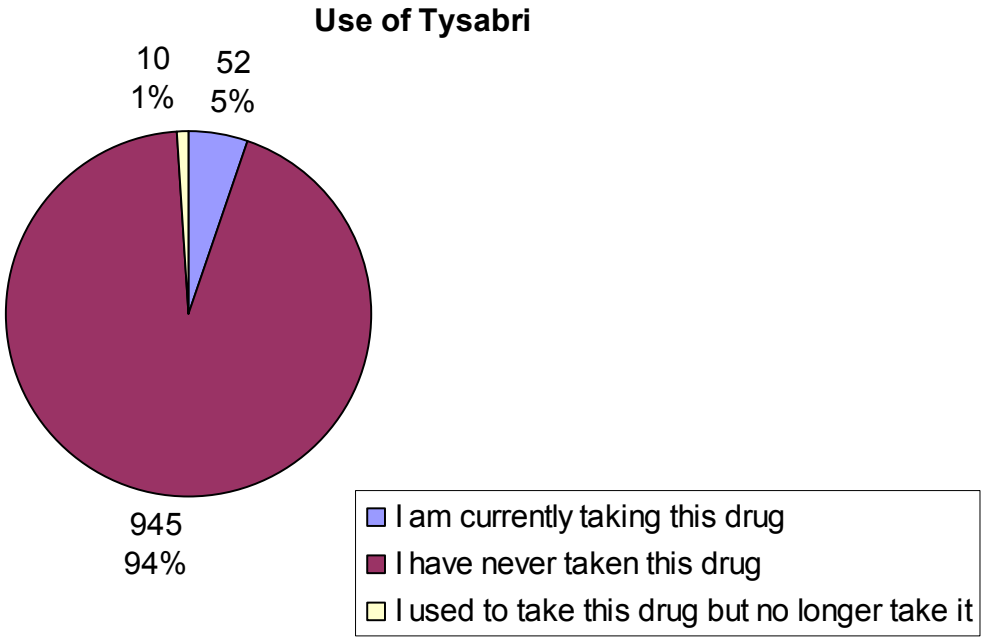
Figure 8



3.2. Taking Tysabri (natalizumab)

Tysabri is the brand name for natalizumab, a disease modifying drug recommended by NICE for adults with "rapidly evolving, severe, relapsing-remitting MS". Unlike injected DMDs, Tysabri cannot be self-administered but is given as monthly infusions by a health care professional.

Figure 9

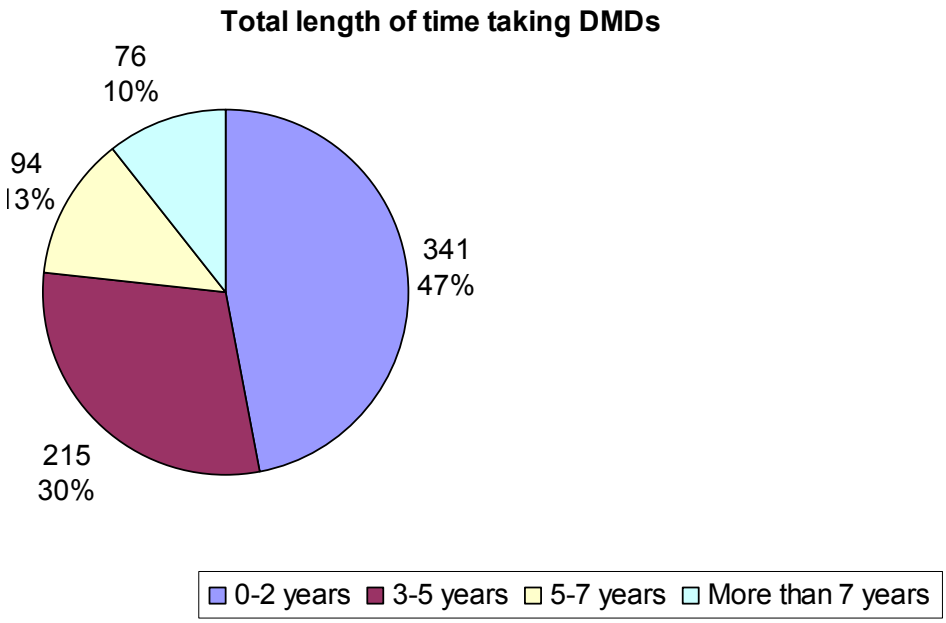


The number of people using Tysabri (figure 9) is lower than the number of those using injected DMDs and this was also reflected in the number of responses to this section – a total of 62. Of the 62, 52 were currently taking Tysabri and a further 10 people had taken Tysabri at some point but discontinued the treatment. Reasons given for discontinuing the treatment were risk of PML, a viral brain infection that can be fatal, and clinician's decision. There has been one large study suggesting that the chance of developing PML for someone using Tysabri for 18 months is around one in 1000. This study looked at over 3400 people taking natalizumab, but they did not all have MS. The risk of PML with Tysabri use increases after 2 years of therapy. The long-term risk is thus not yet known, but it seems this risk might affect decisions about treatment as the following comment exemplifies:

> *"I have been told by my consultant that I have to come off tysabri by the end of this year, so getting new treatments licensed as soon as possible is important because tysabri has changed my life for the better and to lose that is going to be very hard. The only thing is that I have been told that I have to be off tysabri for a minimum of six months so not looking forward to that period with no meds."*

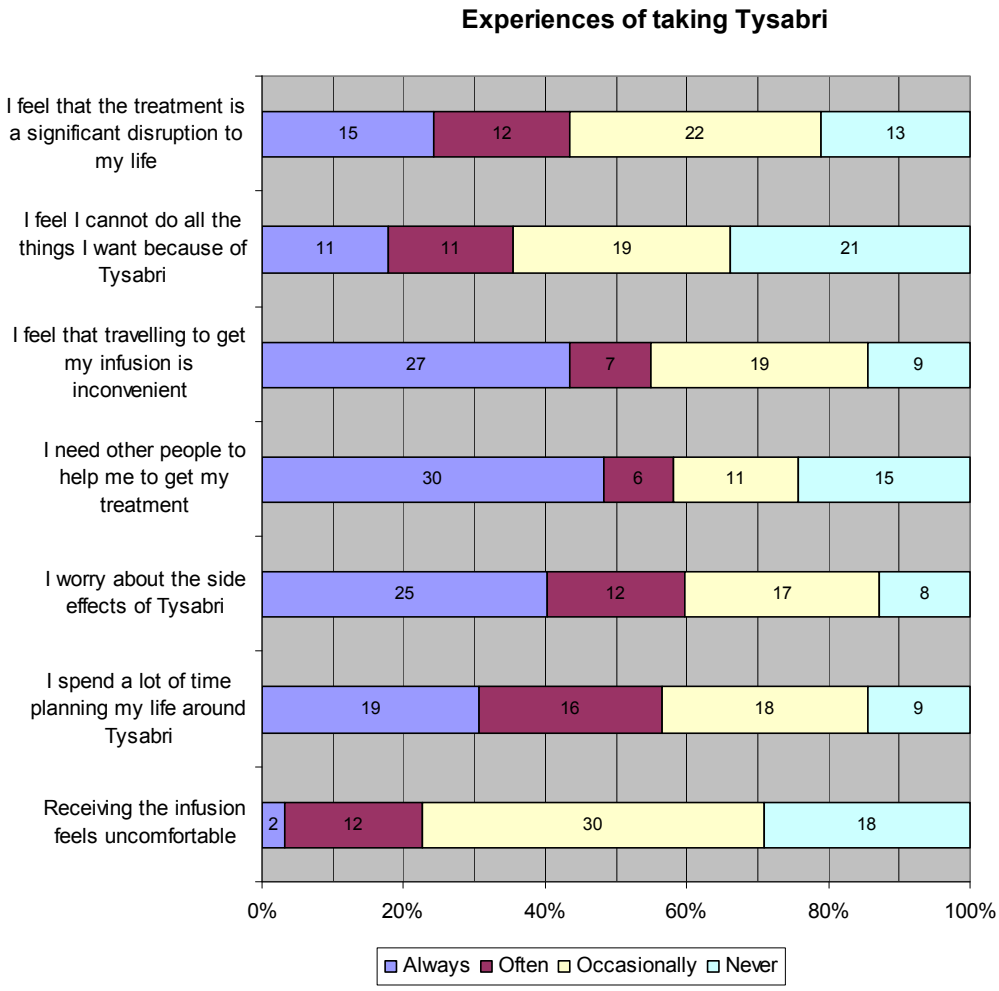
For a break-down of the duration of treatment with Tysabri, please see figure 10.

Figure 10



The respondents were presented with similar statements scoping experiences of being on Tysabri, as in the section about injecting DMDs. The statements were modified to better reflect the practicalities of Tysabri-taking, whilst keeping them as similar as possible to enable comparison (see Figure 11).

Figure 11



When comparing the responses to statements between the two different types of disease modifying treatment, some interesting differences emerge. For the distribution of responses related to Tysabri, please see figure 11.

Practicalities around Tysabri, which is administered monthly by a health care professional, are very different from self-injecting. Receiving one's infusion requires the person to travel to a hospital or a clinic, and this was found to be inconvenient with nearly 50 per cent of respondents finding this to be the case always.

> *"Early days for tysabri. the main difficulty is the travel to hospital (but maybe i'll get used to that) and the time off work required for the treatment. but I remain hopeful."*

> *"Shame I wasn't forewarned of how long the hospital visit would take (patients are told 1 hour infusion + 1 hour obs - first visit was 7.5 hours, subsequent ones never less than 4 - not a problem now I know to take packed lunch + work, but very annoying on first visit when I was unprepared)"*

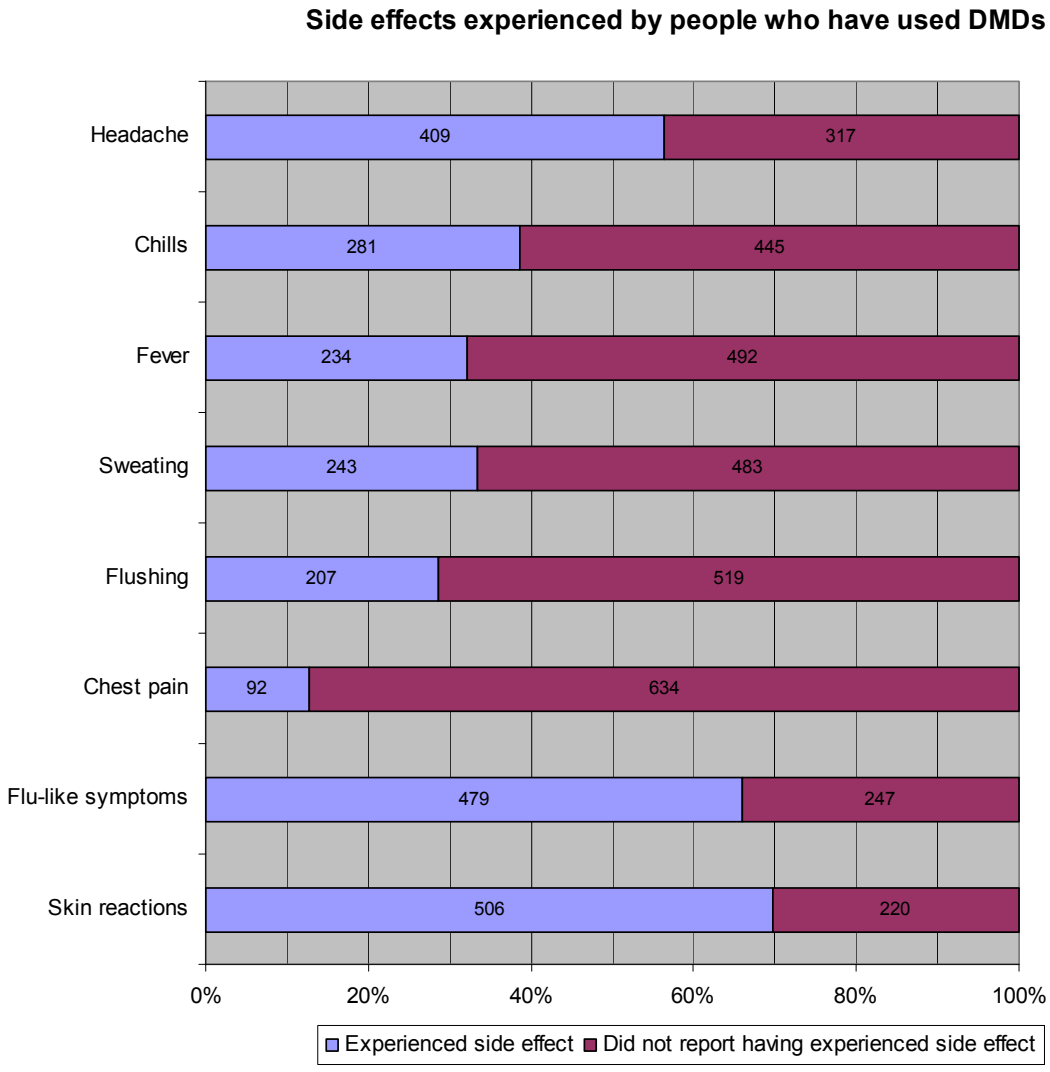
> *"Copaxone has left 'dipping' all over my body, (legs on both sides, buttocks on both sides) and although Tysabri seems to be working, although it does take two days out of my month."*

There are some side-effects, such as shivering, feeling sick or dizzy, that can be experienced during or directly after the infusion. There were similar statements asking about discomfort for each of the treatments – the one asking about feeling uncomfortable when receiving the infusion and the other whilst injecting. 22 per cent of respondents felt receiving the infusion felt uncomfortable either always or often, and this was relatively low compared to the discomfort of the injecting oneself with 56 per cent reporting this to reflect their feeling always or often. Whereas problems and discomfort of injecting were commonly commented, there were no comments made about the discomfort of infusions.

Side-effects

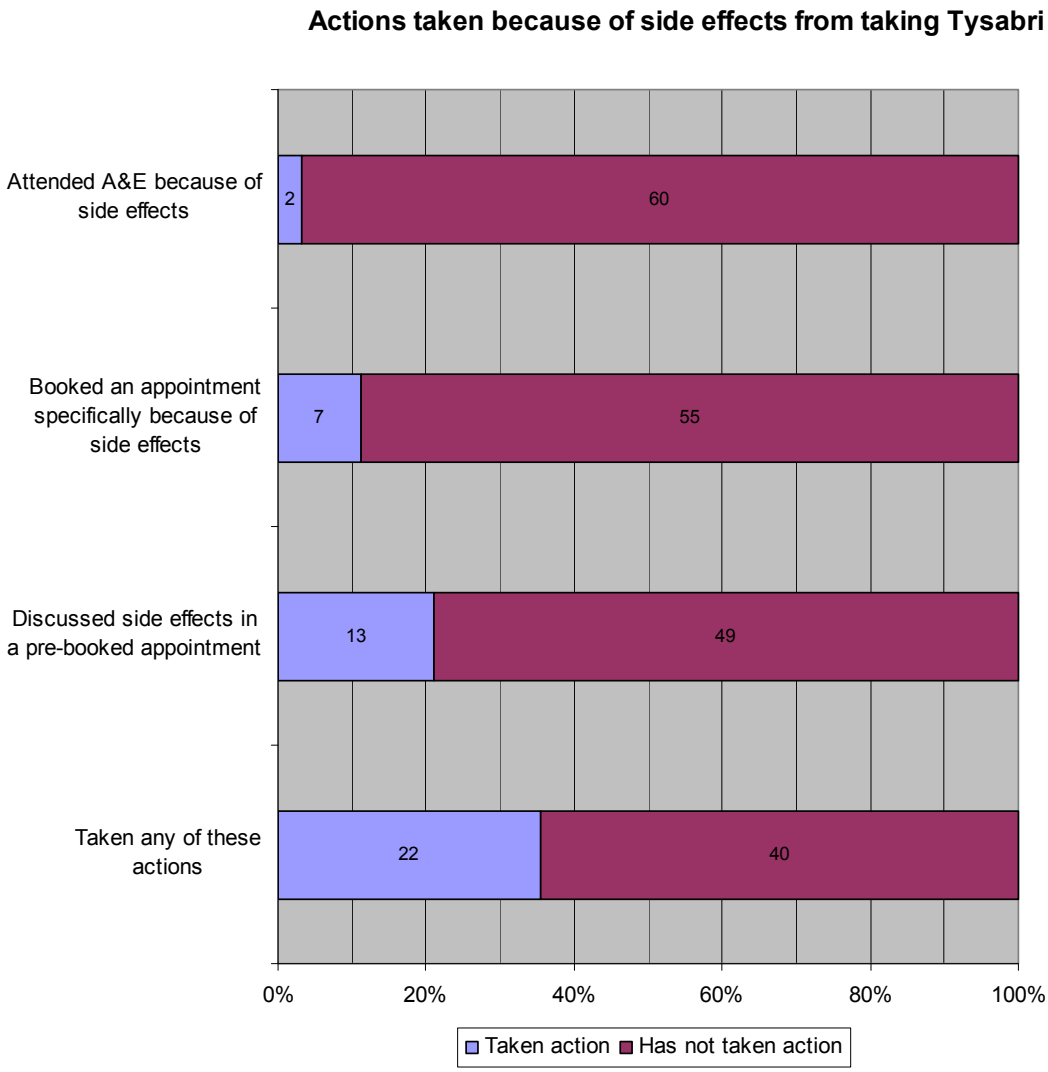
The most common side effects experienced after taking Tysabri are joint pain, fever, tiredness, a runny or blocked nose, sore throat, feeling nauseous, headache and dizziness. All of these side-effects were familiar to the respondents of this survey. The most common side-effects experienced were tiredness (53 per cent of respondents) and headache (39 per cent) (see figure 12).

Figure 12



Some 35 per cent of respondents who had taken Tysabri had sought medical help because of their side-effects (figure 13). This appears to be a lot lower than in self-injected DMDs where 60 per cent of respondents had sought medical help due to side-effects.

Figure 13



Worry about side effects

In addition to the side-effects listed above, taking Tysabri increases the risk of PML, a viral brain infection which can be fatal. In light of this, it is not completely surprising that over 40 per cent of respondents (figure 11) always worry about the side-effects:

> *"I now have very few new symptoms and have only had 2 relapses whilst taking this drug (Tysabri) - although I do worry about PML. As I expected, none of the drugs have improved my disability, but I feel at last that I have plateaued."*

although the fear of PML can be mitigated by being closely monitored:

> *"One of the nasty side effects of tysabri is PML but at least I am surrounded by doctors/nurses when I take drug and I am closely monitored as well."*

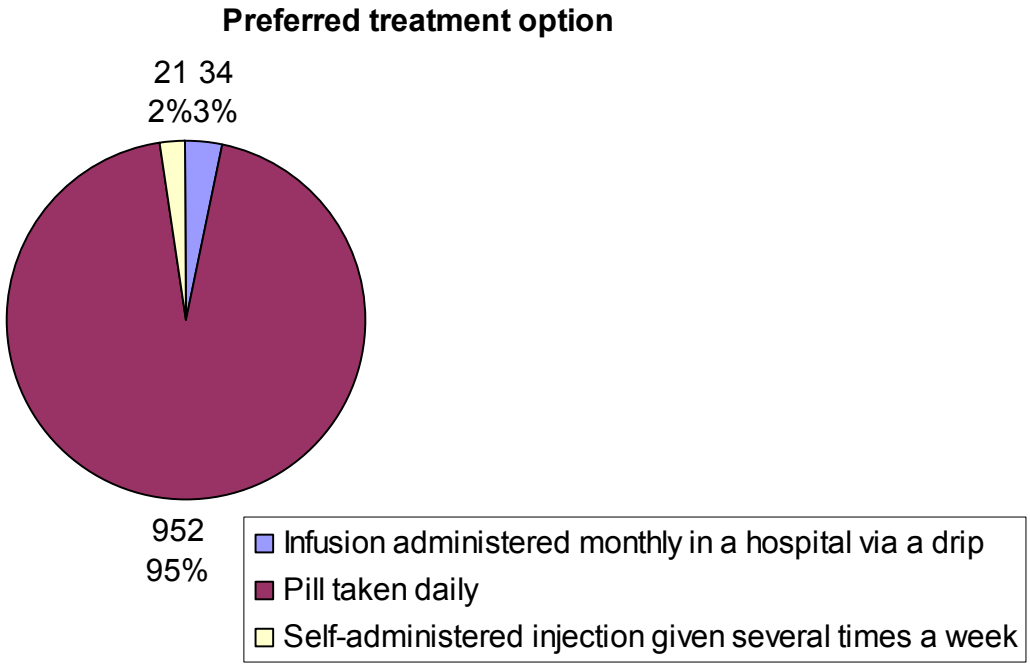
As already discussed, the risk of PML was also commonly given as a reason for discontinuing the treatment. However, despite this, the free comments relating to Tysabri told a very different, more positive story overall compared to those related to injected DMDs:

> *"I was diagnosed with rapidly evolving MS in Feb 2009. I started on Tysabri in March 2009 and I have not had a relapse since. I still have problems with my mobility and speech from my previous relapses but after 17 months of sickness absence from work I am finally stable enough to go back to work. That's all thanks to the Tysabri."*

4. Preferences for disease modifying therapies

The final question in the survey asked for respondents' preference for administering a disease modifying drug if three options were available: an infusion administered monthly in a hospital via a drip, self-administered injection given several times a week and a pill taken daily (see figure 14). Everyone who was qualified to take part in this survey was asked to answer this question, and the total number of responses was 1007.

Figure 14



The overwhelming majority (95 per cent) chose the pill option, giving ease of use, convenience to everyday life and non-invasiveness as reasons for selecting this option:

> *"Taking a tablet I could get on with my every day living, as I should be able to do even though I have MS."*

> *"I am trying to maintain a normal life and stay in employment. My work means that I sometimes need to be away from home. Having to inject at specific days/ times means my flexibility while I am away is much reduced. A drug administered orally would make working life much easier."*

> *"It would be the easiest and least obtrusive method, would fit in better with my lifestyle and would enable me to control my illness in a way which does not draw attention to my disability. It's bad enough living with the illness, coping with the symptoms and trying to get on with life without having to add to the stress with hospital visits and injections."*

Respondents to this survey have shown that the impact of MS is not only limited to people with MS but extends to their friends and family as well. Whilst helpful at times, treatments can also unnecessarily complicate lives and be a constant reminder of one's condition. Just like everyone else, respondents to this questionnaire want to live independently, stay in employment, take care of their families and go on holidays without having to plan, worry and deal with physical and emotional discomfort. It is vital that disease modifying drugs are effective, easy to use and fit around a person's every day life.

> *"If there was a high risk treatment which could potentially cure my MS I would seize the opportunity with both hands as I want to be normal again and not have to endure debilitating relapses several times a year, which set me back so far and mean I have rely on others to help me, when I just want to be able to do the things that everyone else takes for granted."*

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (MTA)

Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment(s).

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to say which treatment (s) you are commenting on.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Multiple Sclerosis Trust

Your position in the organisation: [redacted]

Brief description of the organisation:

The MS Trust is a UK charity dedicated to making life better for anyone affected by MS.

The MS Trust is in contact with over 40,000 people affected by MS - that's people with MS, their families, friends and the health care professionals who help manage MS. Our core belief is that the best outcomes will come from well-informed people with MS making decisions in partnership with their specialist health professionals, and our aim is to support both sides of this partnership as much as we can. We provide expert information to help people with MS manage their own condition, and, uniquely, we inform and educate the health and social care professionals who work with them about best practice in MS treatment and care.

We receive no government funding and rely on donations, fundraising and gifts in wills to fund our services.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

1. **Relapsing remitting MS**

MS is commonly diagnosed between the ages of 20 and 40, at a time when people are developing careers, starting families, taking on financial obligations. Approximately 80% will have relapsing remitting MS (RRMS). Through our enquiry service we are only too aware of the devastating impact MS relapses can have both in the short and long term. We speak daily to

people who are dealing with issues relating to relapsing remitting MS: coping with the impact of diagnosis, choosing which treatment to take, understanding and balancing risk/benefit profiles, dealing with side effects and coping with physical and financial consequences of relapses.

MS relapses are unpredictable in onset, severity, type of symptoms, and duration. Recovery is often incomplete, leading to accumulation of disability with each successive relapse. Residual disability may be apparent, such as impaired mobility, but may also be less overt, such as depression, fatigue, cognitive problems or sexual dysfunction. The more invisible consequences of a relapse can often be overlooked by health professionals, family and work colleagues yet impact on quality of life and capacity to remain in employment as profoundly as more apparent symptoms.

Relapses have a significant impact on the ability to work, leading to time off work (and potentially loss of employment) both for the person with MS and informal carers, resulting in considerable direct and indirect financial burden, both for the individual, their family and the state. They can have a profound effect on a person's daily activities, social life and relationships and present considerable psychosocial and emotional challenges for both the individual and for family and friends.

In a cash-strapped NHS, the reality is that services to support people coping with the effects of a relapse, such as physiotherapy or the provision of equipment or carers, are often limited or non-existent. The quality of and access to care is highly dependent on where someone lives. Individuals contacting the MS Trust frequently report that the urgent access to physiotherapists or occupational therapists necessitated by a rapid onset of symptoms is rarely possible. For example, a caller to our enquiry service reported a 10 week waiting list to see a physiotherapist for treatment of walking problems following a relapse. As well as prolonging the effect of the relapse on someone's life, these delays risk compounding problems, introducing further distress to the individual and cost to the NHS.

Research evidence supports the treatment of people with relapsing remitting MS early in the disease to prevent axonal damage and irreversible disability. Current practice in the management of RRMS is active and acknowledges that even if people with MS continue to have relapses while on therapy, they may still be deriving benefit from the treatment. State of the art approach to treating relapsing remitting MS aspires to minimal or no evidence of disease activity; reducing relapse rates is an essential component of this aim.

2. Clinically isolated syndrome

"CIS was such a hugely stressful time for me. I knew I was high risk of going on to develop MS and the thought of being a sitting duck and having to wait for the next big relapse totally terrified me. I took the bull by the horns and pushed for a DMT which was eventually agreed. I asked for regular MRIs to ascertain any changes and 2 years later was diagnosed with MS following a new lesion. I had not had any symptoms so it goes to show MS can progress and you can be completely unaware. At least I caught mine early."

People who have had a first episode of neurological symptoms, known as clinically isolated syndrome (CIS) describe a feeling of being in limbo, of not knowing what might happen next. Having to wait for the next episode of symptoms creates anxiety and stress. In order to protect their ability to work and maintain family commitments, people with a diagnosis of CIS often want to start early, proactive treatment.

There is now strong evidence that damage to nerves starts very early in the disease course, before diagnosis of MS. Neurologists are able to identify those at high risk of developing CDMS and therefore most likely to benefit from starting treatment with a DMD. Starting treatment at this point has real potential to catch MS before it causes further nerve damage. This will not only delay conversion to clinically definite MS (CDMS) but will also reduce silent MS activity, visible only through imaging or other markers of subclinical disease, preventing further lesions and brain atrophy.

CIS is emblematic of some of the key challenges in RRMS. Diagnostic criteria for MS were revised in 2010 (and are due for imminent review), reflecting the

continued growth in understanding of the underlying pathological processes in MS and giving radiological evidence a greater place in confirming clinically definite MS. More people who would have previously been diagnosed with CIS are now meeting the criteria for CDMS. The 'diagnosis' of CIS is effectively an acknowledgement that the ability to diagnose MS early and swiftly is still limited, but that given the growing evidence of the importance of early treatment with DMDs, people with even a single demyelinating event should have the opportunity to access licensed treatments in order to improve their long term outcomes.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

People with MS want to live a life free from the impact of their disease. Inevitably, the frequency and severity of relapses rank highly for those with RRMS, not just for the disruption and distress they cause, but also because of the risk of residual disability and increased chances of conversion to secondary progressive MS. Ranking the impact of individual symptoms is difficult and ultimately inadequate as the condition varies so widely between individuals.

People with MS are increasingly aware of the significance of reducing or eliminating signs of sub-clinical disease activity in improving long term outcomes.

Remaining in employment is of critical importance to people with MS. Within 10 years of diagnosis, around 50% of people with MS will have left employment, with all the associated financial, social and psychological consequences.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these different treatments and which are preferred and why?

A number of treatment options and DMDs are now available for relapsing remitting MS:

- best supportive care
- first line DMDs including teriflunomide, dimethyl fumarate, natalizumab, and alemtuzumab

Clinical experience of these DMDs is more limited and a number of serious side effects have been reported. For some people, the greater risks of these more recently introduced first-line DMDs are unacceptable.

Through different aspects of our work with people affected by MS, we are aware that a wide range of factors can contribute to an individual's preferences for treatments. The balance between effectiveness of a drug and the risk of side effects are key factors, but other issues will be important such as the number of years a drug has been in routine use, route of administration, tolerability and the impact it has on daily life, family and work commitments or plans to start a family. Shared decision making which takes account of personal preferences and clinical advice will result in a choice of treatment that is best for an individual. This in turn leads to greater adherence and, therefore, effectiveness of the DMD.

People with MS rely heavily on their MS specialist team to provide information and guidance to help with treatment choices. MS teams are skilled and experienced in helping an individual make the choice that is the best match for their level of disease activity, their personal circumstances, their attitude to risk and their treatment goals.

The availability of MS services varies across the UK. These services make up not only the real world foundation of MS care but also represent the components of a definition of best supportive care (BSC), which is the intended comparator (see section 9 for further discussion of the issue of BSC). We wish to stress that access to these services is not uniform and any assumption that they are would misrepresent the reality for many people with MS.

4. What do patients or carers consider to be the advantages of the treatment(s) being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment(s) being appraised.

People with RRMS commence disease modifying drug treatment in order to reduce the frequency and the severity of relapses (including reducing the need for steroids or hospitalisation). They hope to reduce the overall impact of the condition on their everyday life – they want fewer burdensome symptoms, less residual disability and more confidence that they can participate fully in work, social and family life.

They hope to reduce their long term chances of becoming progressively more disabled and the loss of independence that this could bring.

They hope to benefit from the length of experience that prescribers have with these treatments, of managing side-effects and of supporting self-management of the administration of the drugs.

Women with RRMS expect to benefit from the years of experience of supporting women through decisions about starting a family and when to stop and restart treatment with these agents.

Please explain any advantages described by patients or carers for the treatment(s) being appraised compared with other NHS treatments in

England.

The drugs being appraised are established treatments with well-defined safety profiles. MS teams are very experienced with these agents; there is a wealth of clinical experience confirming their general safety and well-established services to initiate and monitor treatment.

Access to some of the more recently introduced DMDs can be delayed due to limited availability of resources such as space at outpatient infusion clinics. There are less likely to be delays in starting one of the beta interferons or glatiramer acetate.

In most cases, these drugs are all well tolerated and require minimal monitoring. There have been significant improvements in injection devices used for the beta interferons and glatiramer acetate, with the result that self-injection is well accepted.

In the event of any unwanted side-effects, a lateral switch is straightforward, with no 'wash-out' period.

If you know of any differences in opinion between patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

We are not aware of any major differences, other than personal preferences.

5. What do patients and/or carers consider to be the disadvantages of the treatment(s) being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)

- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

As covered in our response to section 2, the availability of services which make up best supportive care and which are intended to help people cope with the effects of a relapse, such as physiotherapy or the provision of equipment or carers, is often limited or non-existent.

Please list any concerns patients or carers have about the treatment(s) being appraised.

Some people find side effects, particularly flu-like symptoms and injection site reactions, difficult to cope with. Self-injection can be a problem for those with reduced manual dexterity. Some of the drugs need to be stored in the fridge which can create problems in some circumstances.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

None that we are aware of, other than personal preferences.

6. Patient population

Are there any groups of patients who might benefit more from the treatment(s) than others? If so, please describe them and explain why.

The beta interferons and glatiramer acetate are likely to be of most benefit to those who are risk averse and those who have a relatively low MS activity (individuals with relatively quiescent disease). Pregnancy registries and clinical experience demonstrate their safety for women and men intending to start a family.

Unlike the other DMDs, the beta interferons and glatiramer acetate are also licensed for use in CIS. In the absence of these agents, there would be no licensed treatments for people diagnosed with CIS at high risk of conversion to CDMS.

Are there any groups of patients who might benefit less from the treatment(s) than others? If so, please describe them and explain why.

We would not expect these treatments to be used for people with rapidly evolving severe RRMS or highly active RRMS - other DMDs are approved for these groups.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment(s)?

✓ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment(s) as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Taking any drug in the context of a clinical trial, with greater attention from health professionals, will be different from taking it in routine NHS care. MS nurses and other MS professionals will have a key role in promoting adherence, and continue to have a key role in managing other symptoms that individuals may experience as part of their MS. People will need to be informed about side effects and closely supported to avoid early discontinuation of treatment.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

Relapse rate and relapse severity (measured by need for steroid treatment or hospitalisation) reflect the impact of relapses on people with MS, their families, friends and work colleagues.

Clinical trials tend to focus on the EDSS score as a primary outcome measure. The EDSS is heavily weighted towards ambulation and does not fully capture the wide range of symptoms that people with MS experience, for example, cognition or problems with bladder or bowel. EDSS is a poor

outcome measure for tracking disability early in the course of MS, and particularly so in CIS where symptoms are often subtle, like increased cognitive dysfunction, fatigue or heat intolerance.

If already available in the NHS, are there any side effects associated with treatment(s) being appraised that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

Multiple Sclerosis International Federation. MSIF survey on employment and MS. MSIF: London; 2010
http://www.msif.org/about-ms/day-to-day-living-with-ms/employment-education-and-ms/employment-and-ms-survey.aspx

- Having stable MS was rated as the most important factor enabling people with MS to remain in work. DMDs were listed as one of the top five factors enabling people to remain employed.

Bevan S, et al. Ready to Work? Meeting the Employment and Career Aspirations of People with Multiple Sclerosis. Work Foundation: London; 2011
http://www.theworkfoundation.com/DownloadPublication/Report/289_289_MS3.pdf

- This report highlighted the problems faced by people of working age in the UK and showed that people with MS lose an average of 18 working years, with many dropping out of employment very rapidly after diagnosis.

Giovannoni G, et al. Brain Health: time matters in multiple sclerosis. Oxford Health Policy Forum: Oxford; 2015
http://www.msbrainhealth.org/perch/resources/time-matters-in-ms-report-oct15.pdf

- Expert, evidence-based recommendations aimed at improving outcomes for people with MS. Reviews evidence for early intervention and regular monitoring of disease activity.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

None

Are there groups of patients who would have difficulties using the treatment(s) being appraised or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

None

9. Other issues

Do you consider the treatment(s) being appraised to be innovative?

✓ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

The beta interferons and glatiramer acetate offer an alternative route of administration to other DMDs and a very well-established safety profile.

Are there any other issues that you would like the Appraisal Committee to consider?

The MS Trust is concerned about a number of issues related to this complex appraisal. As we understand it, there are at least three main aspects to this appraisal:

1. Analysis of the data from the RSS observational study, comparing the four agents to natural history data using the analytical model developed during the scheme (best supportive care as comparator). Our understanding is that there is no further analysis planned using any other data or a different analytical model (or a different comparator). If

this is not the case, and additional analysis is planned, stakeholders should be advised of this and how the data from the separate analyses will be brought together into a single decision.

2. Analysis of CIS, which was never part of the RSS observational study, and which is a different patient sub-group from those with RRMS. Our understanding is that there is separate analytical model being developed (based on the RSS model) and used for this analysis. We stress, as we have done in previous submissions, that CIS was not part of the RSS. Stakeholders have little or no information on the adapted analytical model. Further, the diagnostic criteria for CDMS and CIS have changed during the period of the RSS; a significant proportion of participants enrolled in the early CIS trials would now be diagnosed with CDMS. We are not clear how NICE will allow for this.

3. Analysis of Plegridy and whether it will be treated as a biosimilar and so effectively the same as interferon beta 1a, or as a separate agent, therefore needing its own analysis (effectively a single technology appraisal). We are not clear about which approach NICE is planning to take.

Allied to this is the cross-cutting question of what comparator is being used for these analyses – best supportive care is the agreed comparator for 1, but we do not know the comparator(s) for any of the other analyses.

We are concerned that we and other stakeholders are not sufficiently clear about how the analysis for each of these aspects is going to be handled and a risk that, as a consequence, the interests of people with MS or CIS could be adversely affected. For over 10 years, more than 70 MS centres and their staff and over 5,000 people with MS have contributed to the RSS observational study. This analysis is exceptional in NICE's history and the scale of the commitment by the MS community and the complexity of the task for NICE and the team at University of Warwick is significant. To be effective stakeholders in such a large-scale MTA, we need more information about how

this complex and unprecedented analysis is being undertaken. We ask NICE to engage more with stakeholders about this.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- The beta interferons and glatiramer acetate are safe, effective and well-tolerated with a long history of clinical experience
- These drugs enhance the range of treatment options and are particularly suited to people who are risk averse
- These drugs are the only treatments licensed for clinically isolated syndrome with high risk of clinically definite MS
- These drugs increase the chance of people remaining in work and maintaining family and social commitments and quality of life
- The role of the MTA is first and foremost to give clarity and transparency to answer questions posed by TA32.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation:
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

  - ✓ an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

No links or funding

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]

What is the expected place of the technology in current practice?
Is the technology already available?
Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Four disease modifying drug therapies, Avonex, Betaferon, Copaxone and Rebif, have been available since 2002 when the Department of Health Risk-Sharing Scheme (RSS) was set up to establish the cost effectiveness of these medications in the management of Relapsing Remitting Multiple Sclerosis. (Extavia, beta interferon 1b, was developed later and has been approved for use on the NHS since 2009.) When the RSS was set up all of the people living with RRMS who were eligible under guidelines produced by the Association of British Neurologists were given the opportunity to participate in the Scheme and by the time recruitment closed in April 2005, 5,610 patients were assessed as eligible for treatment and enrolled in a monitoring cohort that has since been followed annually in a 10 year observational study.
The RSS has not only provided access to these medications but has also resulted in a significant growth in MS Services that has benefitted all people living with MS. There are currently 72 centres with specialist teams providing MS expertise that also link to the local community teams to support the delivery and monitoring of disease modifying drug therapies.

The technologies under appraisal have therefore formed an integral part of current practice since the establishment of the RSS. They are often a preferred choice for patients who have a low risk tolerance to side effects and do not wish to take a daily oral medication.
.
Since 2002 the treatment options for people living with MS have increased and the Association of British Neurologists have revised the guidelines for prescribing disease-modifying treatments in multiple sclerosis to reflect the impact of these new drugs and the evidence of efficacy (2015). We wish to endorse and support the evidence of our medical colleagues presented in these guidelines.

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

NICE Clinical Guidelines on the Management of MS emphasise the importance of a key person to coordinate and review treatment and care. (*Multiple sclerosis in adults: management NICE guidelines [CG186]*) However they failed to identify the MS Specialist Nurse or Specialist Clinician as a key person in the management of this condition. In their deliberations research evidence was discounted as not robust enough for example: Johnson, Smith and Goldstone (2001) *Evaluation of MS Specialist Nurses (cost effectiveness)* South Bank University London and research

regarding the role of Specialist Therapists, Dix and Green (2013) and the preliminary evidence from the GEMMS study *(Generating Evidence in Multiple Sclerosis Services.)* which was not completed in time for consideration. There was also a failure to extrapolate evidence from other specialties where the Nurse is central to the management and monitoring of the individuals condition (Parkinson's Disease)

During the consultation period many groups commented that the essential role of offering assistance with decisions regarding disease modifying treatments (DMTs) usually undertaken by the Specialist Nurse is not described in the guidance. However the ABN prescribing guidelines state:
"*MS specialist nurses play a vital role in ensuring that the treatment pathways are followed, managing symptoms, and providing education, information and reassurance to patients during and between clinic attendances. In many centres, MS specialist nurses play a key role in supporting patients through the process of making choices about treatment options as well as monitoring patients on these often complex treatments*."
(Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis
Pract Neurol 2015;15:273-279 doi:10.1136/practneurol-2015-001139
ABN Guidelines)
We would therefore contend that the acceptable level of evidence set in the Guideline was unacceptably high and therefore failed to promote current best practice.

The advantages and disadvantages of the technology

These formulations offer a choice to people living with RRMS regarding the way the medication is delivered and the frequency of administration. Some individuals prefer not to be reminded of their condition by the daily administration of a medication and some find that injections are easier to remember being less intrusive to their daily life and easier to manage than the alternatives.
For example the most common side effect is flu like symptoms but these can be mitigated by timing the injections so that these do not occur during times when the individual needs to be alert or at work.

It is our experience that individuals who are newly diagnosed with MS often experience fear and uncertainty around employment. In particular they worry about the job insecurity that arises as a result of frequent relapses. Early intervention and support can reduce some of the fear about the future by reducing the number of relapses an individual experiences. Access to this technology improves quality of life by improving an individual's capacity to remain in work, stay socially engaged and exercise some economic autonomy.

Any additional sources of evidence

"*The Impact of long term conditions on employment and the wider UK economy***"**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]

Bajorek, Hind and Bevan. The Work Foundation (Part of Lancaster University) Feb 2016.
This report highlights the problems of employment faced by people living with 6 long term conditions one of which being MS.

Implementation issues

The implementation of these drug therapies is dependent upon adequate supportive services. Individuals starting injectable medication need training and monitoring to undertake this therapy themselves to feel competent and safe. A cornerstone of the service structure in the delivery of this technology is the MS Specialist Nurse/Clinician.
Helping patients' to choose the best type of medication to suit their needs requires advanced appreciation of the drugs' action. Advise on which treatments are the most suitable may be influenced by, the number of relapses experienced in a specified time frame, the particular needs of the individual and the risks and benefits of each drug.
In addition vigilant monitoring of the patients' response to the drug and a knowledge of how to switch medications safely if necessary is required. The technologies under appraisal are ranked as of moderate efficacy (Category 1 in the ABN guidelines). Depending upon whether an escalation or induction management strategy is being Implemented there may be a need to start a more aggressive treatment or try a different formulation. This can be reported back to the consultant in a timely way if effective monitoring is being undertaken.

The GEMSS study mapped sustainable specialist nurse caseloads against the current provision of MS Specialist Nurses in 2014 and found a shortfall of 62 MS Specialist Nurses across the UK. (MS specialist nursing: The case for equitable provision. Mynors &Bowen MS Trust, Nov 2014) If this shortfall is not addressed it is likely to have a detrimental impact on the safe implementation of these technologies.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:
Dr Martin Duddy

Name of your organisation

Association of British Neurologists

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ☑
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ☑
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? ☑
    - o full member of the Association of British Neurologists
    - o nominated to act on their behalf for this consultation
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:
none

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?

Given current choices, uncertainty on the long term outcomes from specific therapies and lack of direct comparisons, treatment decisions are increasingly based on principles of shared decision making, exploring patient values, lifestyle choices and concerns as part of the process. Differing tolerability and risk profiles affect the acceptability of specific therapies to some patients and physicians. As such, practice varies between and within centres. However, in general:

RRMS:

Newly presenting patient

- Standard presentation – likely to be offered dimethyl fumarate, teriflunomide or IFN/GA. Depending on patient/disease factors, may be offered alemtuzumab. IFN/GA are less often first choices following the advent of the oral therapies
- Rapidly evolving severe (RES) MS: likely to be offered natalizumab or alemtuzumab

RRMS, on treatment

- Tolerance/ safety issues on first line drug – offered switch "within level"
- Treatment judged ineffective (reported relapse usually combined with MR evidence of activity) – escalated to fingolimod, natalizumab or alemtuzumab. Natalizumab would require RES criteria to be met, and patient's JC status will enter into the decision making
- Based on evidence that a poor disability outcome can be predicted by early MR activity, there may be benefit of switching based on MR evidence of activity alone, but options are currently limited by reimbursement criteria to "within level" switch, or consideration of alemuzumab. There may be, potentially, some use of fingolimod in this context, within EU license but outside current NICE/ NHS England guidelines. The threshold for an acceptable level of MR activity in absence of relapse is unclear.

CIS:

CIS as defined in original trials now seen as two groups

- Single clinical demyelinating event with RRMS diagnosed on MR criteria (new lesions on follow up scan or presence of enhancing and non-enhancing lesions on single scan)
    - Likely to be offered treatment if diagnosis of MS established within 12 months.
    - While IFN/GA explicitly licensed for CIS, this group have a "relapsing form" of MS, and DMF and teriflunomide likely to be offered in current practice. A

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

substantial part of the DEFINE and CONFIRM trials were drug naïve RRMS within one year of diagnosis.

- Single demyelinating event without confirmation of RRMS
  - Unlikely to be offered treatment. Potentially followed up beyond first year. Treatment may be considered in certain circumstances if MR evidence of marked disease activity in year 2

SPMS

SPMS evolving in patient already on treatment from RRMS stage

- Likely to continue on existing therapy until shared decision to discontinue. In practice, based on earlier stopping guidelines, it is rare for patients to remain on therapy due to gradual progression reaching EDSS 7 (only able to walk few steps with bilateral support), though in some cases preservation of upper limb and cognitive function will be considered justification for persisting with therapy

Patients presenting de novo, drug naïve with SPMS

- Without reported relapses: unlikely to be offered DMT, ineligible under all guidelines and no trial evidence of benefit
- With reported relapse: may be offered treatment if relapses are a major driver of disability and particularly if concordant MR evidence of active disease. Likely to be younger and with recent onset disease.

Is there significant geographical variation in current practice?

Yes. Prescribing rates and patterns appear to vary (see MS Society “My MS My Needs” survey for England and Wales) (https://www.mssociety.org.uk/sites/default/files/MS%20treatment%20in%20England_0.pdf/; https://www.mssociety.org.uk/sites/default/files/MS%20treatment%20in%20Wales%20WALES%20FINAL.pdf).

No good systematically collected data exists on why this is, but differences in opinion emerge in national meetings. Anecdotally, this seems to be becoming less of an issue with a new generation of consultants trained in the treatment era. Difference in practice, probably driven by attitudes of key local prescribers is apparent in rates up adoption of new therapies between centres.

Are there differences of opinion between professionals as to what current practice should be?

Yes. Differences are expressed on the value of early treatment, the urgency with which therapy should be considered, the level of disease activity (relapse or MR activity) that represents an unacceptable response, and the theoretical merits of an early “induction” approach – use of a higher potency drug from the outset rather than an “escalation” approach. Physician opinion on tolerance of risk varies, and is likely transmitted to patients in shared decision making.

Local experience on the tolerability and apparent efficacy of therapies combined with ease of access and available pharma company support may

explain some differences in the prescribing of superficially similar drugs, clearly noted in the early years of the Risk Sharing Scheme.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

At the time of their launch, there were no alternatives to IFN/GA.

Currently available options are:

- Traditional fist line drugs
  - Betaferon (Extavia), Avonex, Rebif, Copaxone
- Pegylated interferon (recently launched and under consideration in this review)
- Fingolimod
- Teriflunomide
- Dimethyl fumarate
- Natalizumab
- Alemtuzumab
- Mitoxantrone – small amount of off label use, mostly historical now
- Autologous haematopoetic stem cell transplant – small supportive trials and occasional use in limited number of centres, mostly, but not exclusively, in trial setting
- Azathioprine: occasional unlicensed use, mostly historic legacy patients

Restricting comments to the IFN/GA group against the newer drugs in general:

Advantages:

- Familiarity – good experience nationally in discussing the therapies, initiating patients and ensuring good compliance
- Relatively good tolerance and safety – largely free of serious risk
- Emerging evidence on long term efficacy and cost effectiveness (UK RSS)
- >20 years worldwide experience and, long term cohort studies of reasonable quality

Disadvantages

- injectable route, while tolerated in absence of alternative, is clearly not a preference for many patients and is an ongoing cause of lack of compliance and poor persistence on therapy
- some concerns of long term safety with case reports/ series on late occurrence of microangiopathic haemolytic anaemia, particularly with Rebif
- limited long term efficacy which, while RSS may suggest is line with predictions, is clearly not preventing the majority of progression predicted from natural history studies

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Single Technology Appraisal (STA)

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

- Yes, and NICE have recognised this in previous appraisals
- Frequent relapses and MR activity, especially in the early years of the natural history predict a worse long term outcome.
- Relapses or MR activity in the first year of IFN/GA predict a worse response in terms of disability at year 3 or 4 (rev. Sormani et al. Mult Scler 2013; 19: 605–612).
- Achieving "no evidence of disease activity" – freedom from relapse, MR activity and worsening of disability for 2 years on IFN/GA predicts a better outcome in terms of disability at year 7 (CLIMB study; Rotstein et al. *JAMA Neurol.* 2015 Feb;72(2):152-8)

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

- Predictive models for treatment response or harm are poor for this group, despite the length of experience with them

- Rare complication of capillary leak syndrome on initiating IFN is predisposed by predisposed by the presence of a paraprotein

- Pre-therapy prediction of response does not exist, though early response in terms of relapse/ MR activity may identify patients likely to have a poorer medium term outcome in terms of disability, though to date there is no evidence that a therapy switch at this stage improves outcome (rev. Sormani et al. Mult Scler 2013; 19: 605–612).

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

- Initiation will always be in a neurology centre.
- Currently under specialist commissioning, initiation and repeat prescriptions come from secondary care (often through homecare company), with secondary care maintaining responsibility for ongoing blood and MR monitoring, recognition and management of complications
- Increasing complexity of decision making and the burden of monitoring for newer therapies is potentially restricting further the number of centres who can offer the full range of available therapies

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

- Extensive infrastructure was required to allow ready access to these drugs within the UK, with the establishment of assessment and monitoring clinics and the appointment of a network of MS nurses. This was largely funded initially through the UK Risk Sharing Scheme. The structures for ongoing prescribing of IFN/GA are currently in place and shared with other MS treatments, many of which require more input from the secondary care team than this first generation of drugs.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

If the technology is already available, is there variation in how it is being used in the NHS?

- See above

Is it always used within its licensed indications?

- In general, yes. There has been use in <18s outside licence, but otherwise the license is broad enough to cover current use. UK reimbursement guidelines are tighter than the EU licence.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

- Scolding et al. 2015 Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis Pract Neurol doi:10.1136/practneurol-2015-001139
    - Previous iterations of this from 2001 onwards have shaped current prescribing patterns
- NHS England clinical commissioning document [2014]: https://www.england.nhs.uk/wp-content/uploads/2013/10/d04-p-b.pdf

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

- This is an unusual situation of appraising a therapy widely used for 14 years and whose use is being superseded by later technologies.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

- As above, initiation is mostly within ABN guidelines. Switching, escalating and stopping criteria are not fixed but are discussed above

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?

- The effect of these drugs in clinical practice was the basis for the UK Risk Sharing Scheme. The year 6 results of this are in print (Palace J et al. *Lancet Neurology* 2015;14:497) and the full year 10 data will be available to NICE for this appraisal.

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What, in your view, are the most important outcomes, and were they measured in the trials?

- Reducing the accumulation of long term disability is the key measure of success for an MS therapy. RCTs for IFN/GA have been 2-3 years long. Measures reported (2 year relapse rate, short term disability worsening, new MR activity (active T2 lesions, Gd enhancing lesions), reduction in brain volume) have all shown some, but limited and imprecise value in predicting long term disability. The most frequently used scale for disability in MS, the EDSS, is dominated by effects on gait in the later stages, underestimating the effect of cognitive impairment, upper limb function and fatigue on quality of life. It is this uncertainty of extrapolating 2 year data to a disease course of up to 6 decades which has led to the current situation.

What is the relative significance of any side effects or adverse reactions?

- IFN/GA have a long history of use and a well characterised tolerability and safety profile. Side effects and adverse reactions in clinical practice accurately reflect the label.

In what ways do these affect the management of the condition and the patient's quality of life?

- Side effects and perceived lack of efficacy combine to produce poor persistence on these drugs, especially once other options become available (see, for example, Jokubaits et al. *PLoS One*. 2012; 7(6): e38661). LFT and thyroid problems rarely have significant impact.

Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

- MHRA have issued an alert on microangiopathic haemolytic anaemia on interferon-beta
- The extent of lipoatrophy, especially with glatiramer acetate was not appreciated in the short term trials

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

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Single Technology Appraisal (STA)

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

- No concerns in this area

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence?

This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition?

Would NHS staff need extra education and training?

Would any additional resources be required (for example, facilities or equipment)?

- Not applicable to a widely available technology

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Single Technology Appraisal (STA)

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Patient/carer expert statement (MTA)

Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [D809]

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment(s).

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to specify which treatment (s) you are commenting on.

1. About you

Your name: Sarah Bittlestone
Name of your nominating organisation: MS Society
Do you know if your nominating organisation has submitted a statement?

☐ Yes

Do you wish to agree with your nominating organisation's statement?

☐ Yes

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ Yes

- a carer of a patient with the condition?

☐ No

- a patient organisation employee or volunteer?
-

☐ No

Do you have experience of the treatment (s) being appraised (that is, those included in the title)?

☐ Yes

If yes, please tell us which one(s)

Glatiramer acetate

If you wrote the submission from the patient organisation and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

One of the biggest problems with MS, and the hardest to deal with, is the uncertainty: never knowing which, if any, part of my body is going to stop working properly, or at all.

I was diagnosed with MS in 1997 DMTs were new then; I qualified, and was told I could have them, but was actively discouraged and the neurologist told me to 'go away and forget about' my MS.

My symptoms remain primarily sensory; however, one relapse did limit my ability to control my right side. Fortunately this only lasted about a week, but when I regained control, weakness in my leg meant I walked with a stick for 2 years.

I was prescribed Glatiramer acetate (GA) in 2009, following an increase in debilitating relapses, and I believe that it has helped limit relapses, slowed disease progression, and enabled me to remain in employment.

MS has had a huge impact on my life. Fatigue brings on cognitive difficulties with memory and concentration. Pain, balance and muscle spasms all limit my ability to take part in social occasions and be fully effective at work. Fortunately, my employers are very understanding.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

I would love treatment to achieve a cure.

In the absence of this, I believe it's vital to limit disease progression as much as possible, by preventing relapses, and enabling people to live as normal and healthy a life as they can.

Once damage is incurred, symptom management becomes very important. In my case, it has enabled me to continue to work and maintain some quality of life.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

I currently see an MS nurse and a neurologist at least once a year and have done so since 2006. When I was considering DMTs the options were the beta interferons or glatiramer acetate (GA). I chose GA primarily because of the regularity of the injections (daily) so they would be easy to remember, but also because of the lesser side effects and good safety profile. I now use the 40mg injections 3 times per week, and have to programme the days and injection sites into my phone, otherwise I would forget. I have suffered no side effects with either formulation.

In addition, I take tablets to block the sensory and pain signals; these work to an extent, but are sedating so they add to my fatigue.

Knowing that my MS Nurse is only a phone call away if I need help or advice is very comforting.

4. What do you consider to be the advantages of the treatment(s) being appraised?

Please list the benefits that you expect to gain from using the treatment(s) being appraised.

Fewer relapses, meaning less disability

Slower disease progression

No time off work required

Regular dose (was once a day, now 3 times per week)

A well-known, and good, safety profile.

Please explain any advantages for the treatment(s) being appraised compared with other NHS treatments in England.

I chose glatiramer acetate in part because it was a daily injection. I thought this would be easier to remember than other treatments, which seemed to have more complicated dosage regimes. For the risk averse, the safety profile of GA is compelling.

It is delivered at home, compared with other treatments that require attendance at hospital; this means time off work, and the travel involved can be debilitating for people suffering with fatigue.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

5. What do you consider to be the disadvantages of the treatment(s) being appraised?

A clear disadvantage for anyone who doesn't like needles is that GA is an injection;

It needs to be refrigerated, which means that travel plans require extra consideration about facilities. It also means the drug must be given time to come up to room temperature before use.

Going abroad can be more problematic, with security considerations regarding needles in hand luggage.

Please list any concerns you have about current NHS treatments in England.

There are no guarantees that the treatments will work;

The risk of PML with some of the newer treatments is a concern

Availability of DMTs is still variable across the country.

Please list any concerns you have about the treatment(s) being

appraised.

GA is an injection not a tablet.

It needs to be refrigerated.

It needs time to come up to room temperature before use.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

6. Patient population

Do you think some patients might benefit more from the treatment(s) than others? If so, please describe them and explain why.

Do you think some patients might benefit less from the treatment(s) than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment(s)?

No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment(s) as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

If already available in the NHS, are there any side effects associated with the treatment(s) being appraised that were not apparent in the clinical

trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

Depending on the outcome, people with Relapsing Remitting MS could be adversely affected by the recommendations. Ten years of research supports the use of the inteferons and GA for relapsing remitting MS. Unlike the newer treatments, the evidence is available for their safety and effectiveness. If these treatments are unavailable, then the patient's right to choose a suitable treatment will be adversely affected, especially those with a cautious risk profile. If these treatments were withdrawn it would take away a lifeline for some people with MS who have been taking this drug for some time, perfectly safely, and with fewer relapses.

9. Other issues

Do you consider the treatment(s) being appraised to be innovative?

☐ Yes

If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

Although it's been around for a while, there is still some mystery around how these compounds work to mitigate relapses, so they remain innovative.

Is there anything else that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Living with MS is debilitating, increases uncertainty, restricts lives and lifestyle choices.
- It's vital that relapses are prevented and disease progression slowed to improve quality of life and ability to remain in employment.
- GA limits relapses, preventing further damage, thereby slowing progression of disability
- GA and the interferons provide an important option for risk averse patients considering DMTs.
- GA and interferon treatments should be a choice available to everyone with relapsing remitting MS.

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Patient/carer expert statement (STA)

Multiple Sclerosis - interferon beta, glatiramer acetate (review TA32) [ID809]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Denise Murray
Name of your nominating organisation: MS Society
Do you know if your nominating organisation has submitted a statement?

Yes

Do you wish to agree with your nominating organisation's statement?

Yes

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

Yes

- a carer of a patient with the condition?

No

- a patient organisation employee or volunteer?

No

Do you have experience of the treatment being appraised?

Yes

If you wrote the organisation submission and do not have anything to add, tick here (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

My symptoms fluctuate daily, and can also fluctuate within a day. For example, waking up and feeling good doesn't always mean I will feel that way for the rest of the day. If I have a good morning but then get too fatigued, the pain I experience is exacerbated. My main symptoms are fatigue, sensory issues and pain. Certain things cause my symptoms to worsen, such as tiredness, stress and cold temperatures.

Fatigue doesn't just have physical implications, it also causes me to process information more slowly than normal, and at times I cannot think clearly which can be very frustrating.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

The most important outcome for me is stopping progression, which would mean that my symptoms will not worsen. I would also like treatment to ensure I will remain free of relapses. For others who have worse disability levels than me, I would ultimately like a cure to be found, or something that could reverse the person's symptoms to a more manageable and less debilitating level.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

At the time I was diagnosed, three years ago, just injections and intravenous treatments were available. Injections were the first line treatment option so I just had to choose between four injectables and consider which one I thought would be best for me. Luckily, this has worked well for me.

I'm aware that there has been significant progression in the MS treatments available over the last couple of years, but also that with these treatments comes more risk to a patient's health, along with an increased risk of side effects. I understand that this is part and parcel of these types of medication but it would be great if the risk of side effects and other health issues could be reduced by treatments, while also remaining effective.

In terms of care, I see my MS Nurse about twice a year and my Neurologist about once every 18 months. Due to demand, I don't see the Neurologist as often as I am supposed to. In addition, through doing a lot of research about MS, I became aware that remaining relapse free doesn't necessarily mean the illness is not progressing, so I ensure I receive an MRI once a year. This is something that concerns me as it's up to me to chase this up and ensure I receive it, and I think it's very important that MRIs are used with DMDs to ensure that it's not just outward signs of MS progression that are being measured. I think it's important that the NHS takes control of this and ensures everyone with MS receives an annual MRI, as at the moment this is definitely not the case and could have serious long term implications for individuals. If a person's illness is processing without them experiencing relapses, and this was picked up from a MRI, they would then be able to make an informed decision about continuing with their current DMD or changing to another. Due to the number of new medications in the last couple of years, there are various options now available to people.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability

- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

I have taken Beta Interferon (Avonex) weekly injections for the last three years, and began this treatment shortly after I was diagnosed with MS.

I had relapsed three times in six months before I went on Avonex, and since I started the injections, I've been relapse free. I also find the pen easy to use as it's automatic and I can self inject at home, so this is an advantage for me too in comparison to a standard syringe or having to go to the hospital for treatment. I chose Avonex as I like the fact that I only have to do it weekly, and I was impressed with trial results. I've been lucky that I haven't suffered any side effects and this treatment has worked well for me from the start.

Before taking Avonex, I wasn't in a good place physically or mentally. The diagnosis of MS was quite a shock, but having three relapses had also taken it's toll. I had fears that if I was going to relapse every couple of months, that there was no way I would have been able to cope with that. I was also worried that I was just going to keep getting worse and that my life would change dramatically, and I wouldn't be able to do the things I would normally do. I had always been fit and active but at that time I couldn't even stand in a yoga class without shaking profusely. I also experienced a lot of pain when I walked.

Since taking Avonex, and making some lifestyle adjustments (eg. diet, supplements, types of exercise, meditation), my health improved significantly. So much so that a few months later, I began training for a half marathon and an open water swim. I managed to complete both these events and I believe Avonex played an important role in helping me get back to good health. In turn, this had a positive effect on my family and friends, particularly my husband and parents who had struggled greatly when I was suffering. I'd always been the healthy, fitness obsessed one so they found it very difficult to see me the way I was.

In the few months after starting Avonex, along with taking specific neuropathic pain medication, my symptoms improved and the levels of pain I experience now are much more manageable than they once were. Symptoms do fluctuate but for me it is manageable, and for the most part I can do what I want to do, and this is priceless.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

While there are other treatments that have now shown more impressive results in trials, with these come an increased risk of other health problems or side effects. Beta Interferon is an important first line treatment, for many people it works and can be incredibly effective in improving quality of life, symptoms and relapse rates, along with disease progression.

It gives people their lives back without having the worry of other serious consequences.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

I know that some people experience flu like symptoms after taking their injection. I take paracetamol and ibuprofen before and after my injection and do not experience any negative side effects. On one occasion, I forgot to take the paracetamol and ibuprofen after my injection and I woke up during the night with awful flu like aches. I never forgot again! I think it's therefore important to ensure everyone knows that this approach can actually help, it was recommended to me by the Avonex Nurse.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)

- any other issues not listed above

Flu like side effects are definitely a side effect for some, and I know this can be intolerable. As mentioned above, there may be approaches that can help manage these symptoms, though this might not work for everyone. I'm sure these side effects have a significant effect on people on a weekly basis, and no doubt have family, social and workplace implications.

With all MS medications though, it's clear that DMDs, like the illness itself, are very individual. What works for one person may not suit another, therefore it's important that a wide range of treatments and choices remain available.

The portability of the treatment can be an issues, for example travelling for work or going on holiday. I'm going abroad for 4 months so getting this amount of refrigerated injections with me on a plane has been difficult to arrange. However, mostly people will only travel for a week or two so this is not a huge concern.

Please list any concerns you have about current NHS treatments in England.

Please list any concerns you have about the treatment being appraised.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

As mentioned, I think that all MS treatments work for some people and not for others. Many people have to change treatments several times before they find one that is suitable for them. In my experience, and from information I've read, I believe that Beta Interferon is an important first line DMD due to it's low risk level and proven track record.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

Some people may experience side effects therefore the treatment may not be suitable for them. Also, there are people who may have a fear of needles and be unable to use the treatment at all, or others may have to rely on someone injecting for them if they can't face self injecting.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

□ Yes

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

I have been lucky enough to remain relapse free since beginning the treatment, and also MRIs have shown no significant progression therefore my experience has actually surpassed that of the results shown in some of the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

As the treatment is still relatively new in medical terms, I think that long term results should be measured in the coming years. Long term side effects or implications are not known, which is an important outcome, but one that may remain unknown for a while.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Not that I am aware.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

9. Other issues

Do you consider the treatment to be innovative?

Yes

In my opinion, all DMDs for MS are innovate. There are a variety of different options - injections, tablets, intravenous methods, and this is important to provide different options to people in terms of risk, side effects and how it works for each individual.

Is there anything else that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Quality of life can improve significantly
- Positive effect on symptoms
- Reduces relapse rate
- Reduces progression
- Low risk

The Committee's specification for further work to be carried out by the Assessment Group for beta interferon and glatiramer acetate for treating multiple sclerosis [ID809]

Project Number	ID809
Project title	Beta interferon and glatiramer acetate for treating multiple sclerosis
Background to below requests for companies and Assessment Group	The committee was unable to make recommendations for beta interferon and glatiramer acetate for treating multiple sclerosis. The committee noted that prior to the 1st committee meeting, on 2 November 2016, the Department of Health submitted cost-effectiveness evidence for the technologies included in the Risk Sharing Scheme. The committee agreed that it preferred these estimates but noted 2 concerns: • The Assessment Group had been unable to verify the estimates in the source documents. • Plegridy was not available when the Risk Sharing Scheme was established. The appraisal committee agreed that further analyses were required from the Assessment Group before it could make recommendations. **The committee's preferred assumptions and current conclusions (from the 1st appraisal consultation meeting – 2 November 2016) were:** • Preferred the risk sharing scheme clinical data, supplemented by the trial data

	• To apply treatment 'waning' (i.e. 50% reduction after year 10) • To use the Department of Health's approach to estimating backward transitions in Expanded Disability Status Scale health states • To use the relative relapse and discontinuation rates as in the assessment group's model • To apply UK list prices for each drug (unless a PAS or CMU price is available) • Include the disutility to carers • To apply all of the above points to the assessment group's clinical isolated syndrome model, where appropriate On the basis of the information available at the 1st appraisal committee meeting (2 November 2016), the committee could not conclude which treatment was the most clinically effective. Based on cost effectiveness, the committee were unlikely to recommend beta interferon but were more likely to recommend glatiramer acetate for relapsing-remitting multiple sclerosis and clinically isolated syndrome.
Information requested from Department of Health (to be incorporated into the Assessment Group report)	The appraisal committee have requested the following information from the Department of Health: • Information about the market share of each beta-interferon and glatiramer acetate from the Risk Sharing Scheme (RSS) • Prices and calculations used to compute the weighted average cost using the list-price (i.e. £8,000)

	• A definition of the 'implied hazard ratio' used in the in the RSS model • The implied hazard ratio and the annualised relapse rate based on the year 10 RSS data for Betaferon • The pooled implied hazard ratio and a pooled annualised relapse rate based on the beta interferons alone (i.e. excluding glatiramer acetate) • For the sensitivity analyses applied in the Department of Health cost-effectiveness analysis using the RSS model and year 10 data: · The implied hazard ratios used in the analyses (pooled and for each technology) · Transition matrices specified in Variant C4
Analyses requests from the Assessment Group	NICE requested the following information and analyses from the Assessment Group: • To critique the information requested from the Department of Health (see above) • To reproduce the ICERs calculated by the Department of Health prior to the first appraisal committee meeting • Provide the following cost effectiveness scenario analyses (incremental and pairwise) for beta interferon and glatiramer acetate 1. Applying the committees' preferred assumptions to the model (please see above), and using the Risk Sharing Scheme data with: a. Individual implied hazard ratios for all drugs b. Pooled implied hazard ratio of all drugs c. Pooled implied hazard ratio of all beta interferons 2. Sensitivity analysis of: a. Costs of EDSS states b. Cost of relapse

Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence: Addendum 4

Title: Clinical and cost-effectiveness of beta interferon and glatiramer acetate for treating multiple sclerosis

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Declared competing interests of the authors

The authors have no conflicts of interest.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

All CIC (Commercial in Confidence) data has been highlighted in blue and underlined, all AIC (Academic in Confidence) data is highlighted yellow and underlined

This report should be referenced as follows:

Contributions of authors

GJMT coordinated the project, led the review of clinical effectiveness and led the drafting of the report. PA led the review of cost effectiveness, the critique of the RSS submission and the economic modelling and contributed to drafting the report. XA co-led the review of clinical effectiveness and contributed to the drafting of the report. HM and JM contributed to the economic evaluation work and contributed to drafting the report. RC contributed to the reviews of clinical and cost effectiveness through search and information specialist support and to the drafting of the report. AK and SL contributed to the review of clinical effectiveness and to the drafting of the report. CC and OC contributed as clinical experts and to the drafting of the report. JP and JR contributed to the review of clinical effectiveness and to the drafting of the report. HF contributed to drafting the report. AC supervised the project and contributed to the drafting of the report.

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1 Introduction

In this document, we first describe the different addenda that we have submitted to date. We then describe the price changes which were made during the course of the appraisal by the Department of Health (DH). We then explain the implied hazard ratio. We document our validation and replication of the ICERs submitted by the DH on 1 November 2016, with additional information supplied by the DH on 10 January 2017. We present our analyses for relapsing-remitting multiple sclerosis (RRMS) following the committee's preferred assumptions, including sensitivity analyses on costs from the UK MS Survey, and then undertake the same for clinically isolated syndrome (CIS).

Next we discuss the challenge to this appraisal of multiple relapse management costs, and show that relapse management cost does not meaningfully impact on the calculated ICERs in this appraisal. We provide an account of approaches to modelling pegylated IFN β-1a 125 μg SC every two weeks (Plegridy), and explain why, given the committee's preferred data source (the Risk-Sharing Scheme), we are not able to include this drug in some comparative analyses.

Finally, in an appendix, we present the analyses from our original report arising from the late-breaking correction to the pooled prices as supplied by the DH in November 2016. These analyses follow the convention of the original report; that is, they use our original definition of 'base case' instead of the one used here. However, it should be noted that they also use the updated pooled price of £8,000.

2 Account of differences between the addenda

This is the fourth addendum we have submitted over the course of this appraisal. To assist committee members in understanding what has changed over the previous addenda, we have prepared the table below (see Table 1).

Table 1 Differences between the addenda submitted to NICE

Number	Date submitted	Reason for addendum
1	12 Aug 2016	This addendum replicated relevant economic analyses as presented in the main report, but included the various pricing arrangements set up for each drug under the RSS. In this addendum we considered price reductions, infrastructural contributions, and a combination of price reductions and infrastructural contributions. We note that the committee decided in AC1 that these price reductions and contributions were not probative as they did not constitute a PAS.
2a	14 Oct 2016	Addendum 2a relates to non-confidential analyses. Addendum 2b parallels Addendum 2a but contains confidential analyses incorporating price reductions and infrastructural contributions. These addenda included presentation of all relevant models including both carers' disutilities and time-varying treatment effects.* Carers' disutilities and time-varying treatment effects were not part of the AG base case in the full AG report, thus only some models were presented as appendices. These addenda also included a sensitivity analysis requested by NICE that used pooled intervention effects from the AG meta-analysis of drugs included in the RSS and individual drug costs. Finally, these addenda allowed for the correction of some incorrect values for parameters provided to the AG.
2b	17 Oct 2016	
3	1 Nov 2016	This addendum provided additional sensitivity analyses in advance of AC1. In particular, the AG presented analyses that substituted the pooled intervention effects from the AG meta-analysis for time to progression in the base case model and used alternative cost estimates for EDSS health states derived from Karampampa et al. (2012).[1]
4	3 Mar 2017	This (current) addendum reflects the revised specification circulated by NICE. We describe the price changes which were made during the course of the appraisal by the DH, explain the implied hazard ratio, and document our validation and replication of the ICERs submitted by the DH on 1 November 2016 including additional information supplied by the DH on 10 January 2017. We then present our analyses for RRMS and CIS following the committee's preferred assumptions and integrating price changes, and including sensitivity analyses on health state costs from the UK MS Survey. We discuss the challenge to this appraisal of multiple relapse management costs, and show that relapse management cost does not meaningfully impact on the calculated ICERs in this appraisal, provide an account of approaches to modelling pegylated IFN β-1a 125 µg SC every two weeks (Plegridy), and explain why, given the committee's preferred data source (the Risk-Sharing Scheme), we are not able to include this drug in some comparative analyses. Finally, in an appendix, this addendum provides revisions to models presented in the original report. These errata arose due to an incorrect pooled price for DMTs as provided to the AG in the year 10 model at the start of this appraisal.

*The RSS submission also included a sensitivity analysis using a 'time varying model' to take account of a perceived lack of fit of the RSS in taking account of trajectories of patients with higher EDSS at baseline. This model has two sets of transition probabilities, one for years 0-2 and one for all subsequent years.

3 Price changes

The assessment group received electronic models from the Department of Health (DH), which were used to assess the cost-effectiveness of disease modifying therapies (DMTs) compared to best supportive care. The AG was notified of these models on 1st April 2016. In these models (DH base run model without time-varying treatment effects and DH base run model with time-varying effects), the weighted average annual cost for DMTs (beta interferons and glatiramer acetate) was stated as £7,300. As part of the appraisal process, the assessment group undertook scenario analyses which used this aggregate cost. However, based on correspondence, and subsequent documents from the DH, on 1st November 2016 the assessment group was informed that the weighted average annual cost of DMTs under NHS prices was £8,000, and under list prices as £8,444. The AG notes that these revised costs were provided after the AG's initial analyses were presented to NICE and sent for consultation.

We requested clarification on how this cost had been derived in order to provide a critique. On clarification, the DH provided information on the proportion of people being treated with different DMTs in the Risk Sharing Scheme (RSS) (see Table 2), and suggested that the weighted average cost per person per year was £7,986, which they had rounded to £8,000. It should be noted that this cost includes '*the discounts agreed between the department of health and the companies at the outset of the scheme (and published in the 2002 Health Circular) but not the infrastructure allowance.'* The proportions *'excluded patients with SPMS* [secondary progressive multiple sclerosis] *at baseline and … all scores after a switch to another DMT.'* We refer to this price of £8,000 as the 'NHS price'.

Table 2 Proportion of people receiving DMTs along with the 'NHS price' and list price

Disease modifying therapy	**Proportion of people N (%)**	**'NHS price' following Y8 price changes (£/pa)[a]**	**List price (£/pa)[b]**
IFN β-1a 30µg IM once weekly (Avonex)	[redacted]	[redacted]	8502
IFN β-1b 250 µg every other day (Betaferon)	[redacted]	[redacted]	7259
IFN β-1a 22µg SC three times a week (Rebif)	[redacted]	[redacted]	7513
IFN β-1a 44µg SC three times a week (Rebif)	[redacted]	[redacted]	10,572
Glatiramer acetate 20 mg SC three times weekly (Copaxone)	[redacted]	[redacted]	6701
Weighted average cost		7986	8444

IFN, interferon; IM, intramuscular; N, number; NHS, National Health Service; pa, per annum; SC, subcutaneously

a *Including where relevant the discounts agreed between DH and the companies at the outset of the scheme (and published in the 2002 Health Circular) but not the value of the 'infrastructure allowance'*

b Values taken from the Assessment Group's report, except for Rebif 22 (£48.16 per syringe x 3 per week x 52 weeks)

Additionally, the DH derived an average price of £8,444, based on the National Health Service (NHS) list prices and the proportion of people treated with DMTs in the RSS. These costs appear to have been derived correctly. As a result of this latter alternative cost, the assessment group has undertaken further scenario analyses (using this cost of £8,444) to explore the impact on the base-case incremental cost-effectiveness ratio (ICER), using the without treatment waning model and the treatment waning model. We refer to this price of £8,444 as the 'list price'. This is the price we now use in the majority of AG analyses that consider pooled drug costs, but not the errata contained below.

4 Description of the implied hazard ratio

The aim of this short note is to discuss our interpretation of the 'implied hazard ratio', which was used in the RSS to show the clinical effectiveness of DMTs for treating people with relapsing remitting multiple sclerosis (RRMS). First we provide a brief summary of the RSS. Second, we define the terms hazard and hazard ratio, which are commonly used in survival analysis, then we provide our interpretation of the 'implied hazard ratio'. The AG notes that it was unable to achieve complete clarity on how the Department of Health derived and used the implied hazard ratio until late-breaking clarifications after AG analyses were submitted.

Risk sharing scheme

In 2002, the Department of Health in collaboration with the UK MS Trust, MS Society and participating pharmaceutical companies launched the RSS to ensure that people with RRMS who met the Association of British Neurologists (ABN) criteria had access to DMTs through the UK National Health Service (NHS) in a cost-effective manner (Palace et al., 2014[2]). Between 2002 and 2005, over 5000 people with RRMS were enrolled into the RSS with the aim of measuring disease progression annually over a 10-year time horizon (Palace et al., 2014[2]). In the RSS, annual data were collected on expanded disability status scale (EDSS) levels, and people were followed-up, even when they discontinued treatment (Boggild et al., 2009[3]). As set out at the beginning of the RSS, DMTs were required to maintain a £36,000 per quality adjusted life year (QALY) over a 20-year time horizon; individual DMTs not within 10% of their clinical effectiveness targets subsequently incurred a price reduction to the NHS (Boggild et al., 2009[3]). The RSS was overseen by a steering group which comprised representatives from key stakeholders and independent scientific advisors. A scientific advisory group which included epidemiologists, health economists and neurologists provided technical advice and monitored the conduct of the scheme. To date two studies (Boggild et al., 2009[3] and Palace et al., 2014[2]) have been published in peer-reviewed journals based on information collected at two years and six years, respectively.

Below we discuss the methods used to determine if a price reduction was warranted; but first we define hazards, hazard ratios, and the 'deviation' measure used in the RSS.

Hazards and hazard ratios

In survival analysis, survival patterns (time-to-event) are compared using the hazard between different groups over the duration of the study (Kirkwood and Sterne, 2005[4]), and presenting the results in the form of a hazard ratio. The hazard is the rate of failure per unit of time for each group being compared. For simplification purposes here, we are interested in the hazard in group A (exposed) at time *t+1* and the hazard in group B (unexposed) at time *t+1*. The hazard ratio indicates how quickly a patient would expect to have an event compared to another patient. A hazard ratio less than 1 in group A as compared to group B means that group A will take longer to have an event. Conversely, a hazard ratio greater than 1 in group A as compared to group B means that group A will have the event faster on average. In MS, an improvement of a drug compared to standard care would be represented by a hazard ratio of less than 1.

With respect to the RSS, we are interested in comparing the clinical effectiveness of using DMTs to reduce the progression of disability in people with RRMS (the group exposed to DMTs) compared to people who receive standard care (unexposed). Because the RSS did not follow up an untreated cohort, the British Columbia multiple sclerosis (BCMS) natural history cohort was used to provide information on disease progression in people with RRMS receiving standard care.[2] In the RSS, the main outcome measure was *'the change relative to baseline of a weighted sum of the proportions of patients who have progressed to each EDSS score; the weighting factors will be loss of utility of patients in each EDSS, relative to the utility of 1 for perfect health.'* In other words, it was the summation of the proportion of patients across all EDSS levels at time *t*, and weighted for utility.

Cost-effectiveness deviation measure

In order to maintain their 'cost-effectiveness', companies were penalised if their DMT had not met their targeted outcomes and adjustments were made to the prices paid by the NHS. These methods for price adjustments were not transparent to the assessment group but were based on a *'deviation'* measure. The deviation measure was derived individually for each DMT and in aggregate, and was defined as *'the difference between actual and expected benefit expressed as a percentage of expected benefit.'* A positive deviation suggested that the actual benefit conferred by the DMT was less than the expected/projected cumulative benefit. A negative deviation suggested a greater benefit than expected. If there was a positive deviation greater than or equal to 10% this led to a price adjustment (RSS SAG, overview of the Year 10 analysis, dated March 2016).

If a price adjustment was required, *'the new price is to be calculated in a way which reflects the actual performance of the DMT in reducing the rate of progression in the RSS cohort, rather than the rate assumed on the basis of the original randomised controlled trials (RCTs).'* This summary performance measure is called the *'implied hazard ratio'*.

Defining the implied hazard ratio using a 'clinical' deviation measure

Disability progression in both the RSS cohort and the BCMS natural history cohort can be summarised by means of a transition matrix. A transition matrix is a table that includes the probabilities of a person moving to another EDSS state (or staying in the current EDSS state) at time *t+1* based on the EDSS score of the person at time *t*. The implied hazard ratio could be calculated by comparing the transition matrices to find a value that, when multiplied by the transition probabilities in the EDSS matrix, would lead to a difference in disability progression of zero between the two matrices. The specific value of the implied hazard ratio was found by using *'a range of hazard ratios and interpolating, in order to find the value for which the deviation measure* [between the two transition matrices] *becomes zero.'* The implied hazard ratio could be derived both in aggregate form and for each individual DMT included in the RSS. Another way of understanding the implied hazard ratio is as the value that was used to convert the observed disability progression in the RSS to that expected from the BCMS cohort.

In the RSS models submitted, the 'implied hazard ratio' was reported as 0.7913. To our knowledge and understanding this represents the hazard ratio from which the deviation measure at year 10 was zero. Two decision analytical models were submitted by the Department of Health to account for the possibility that the effectiveness of DMTs reduced or 'waned' over the course of time. One model assumed 'no waning' of the treatment effect (i.e. the treatment effect remained constant over the duration of the model) and the other model assumed a 'waning' effect, represented by a 50% reduction in the treatment effect from year 11 onwards, for the duration of the model time horizon. In the models, the implied hazard ratio was used to adjust transition probabilities to reflect the benefit of treatment with DMTs by changing the rate at which people were assumed to progress to more severe health states. Slower progression indicates a benefit in that reduces loss of QALYs.

In the BCMS natural history cohort, people appeared to have undergone 'backward transition' or improvement by moving to less severe EDSS levels. However, this may be a result of *'measurement error and/or [temporary] recovery from relapses' (SAP year 10 data)*. In the analysis undertaken by the DH, it was assumed that DMTs had no impact on backward transition to less severe health states. The AG agrees that this is a reasonable assumption.

5 Replication of the DH ICERs, including discussion of any differences arising

In this section, we discuss and aim to reproduce the ICERs submitted by the Department of Health. In our critique, we have examined the new inputs and the rationale for these variants.

DH ICERs using 'transparent NHS prices'

The DH submitted ICERs using 'transparent NHS prices', that is, the prices charged for each drug after price changes arising from the Year 8 RSS analysis. In these models, carers' disutilities are included and discontinuation rates are set at 5% per year. The pooled price for DMTs in this analysis was £8,000. We replicate and validate these ICERs below (see Table 3 and Table 4).

Table 3 DH ICERs using 'transparent NHS prices' and the without treatment waning model

DMTs	Department of Health			Assessment group		
	Net cost (£)	*Net QALYs*	*ICER (£ per QALY)*	Net cost (£)	Net QALYs	ICER (£ per QALY)
All RSS DMTs	*31,684*	*1.047*	*30,262*	31,700	1.047	30,300
IFN β-1a 30µg IM once weekly (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1b 250 µg every other day (Betaferon)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44/22 µg SC three times a week (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg SC three times weekly (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4 DH ICERs using 'transparent NHS prices' and the treatment waning model

DMTs	Department of Health			Assessment group		
	Net cost (£)	*Net QALYs*	*ICER (£ per QALY)*	Net cost (£)	Net QALYs	ICER (£ per QALY)
All RSS DMTs	*35,695*	*0.900*	*39,648*	35,700	0.900	39,600
IFN β-1a 30µg IM once weekly (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1b 250 µg every other day (Betaferon)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44/22 µg SC three times a week (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg SC three times weekly (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AG comments: As part of the technology appraisal, the assessment group received reports and electronic models from Biogen, Merck, Teva and the DH. However, the assessment group did not receive a submission from Novartis/Bayer for IFN β-1b 250 µg every other day (Betaferon/Extavia). Through correspondence with the DH, the AG has now been provided with the implied hazard ratio

([redacted]) and the annualised relapse rate ([redacted]) for IFN β-1b 250 µg (Betaferon/Extavia). We have included these values in our analyses, and the results from the assessment group are in line and agree with those provided by the DH for both the 'without treatment waning' model and the 'treatment waning' model. We note that the DH model included combined estimates for both doses of IFN β-1a SC three times a week (Rebif), 44 and 22 µg, weighted by their use in the RSS. To replicate the ICERs, we estimated a weighted average of the implied hazard ratios and of the annualised relapse rates for this DMT. We regard that any differences are likely due to rounding of the clinical effectiveness parameters, as the AG was only provided these to two decimal places.

DH ICERs using 'transparent NHS prices' and incorporating AG modifications to the RSS model

The DH further submitted ICERs using the prices as above, but patterned after the AG's base case from the original report. In this model, carers' disutilities were excluded and discontinuation rates were estimated for each DMT based on the AG meta-analyses. These ICERs, and the AG replication of these ICERs, are presented in Table 5 and Table 6.

Table 5 DH ICERs using transparent NHS prices, incorporating AG modifications to the RSS model and without treatment waning

DMTs	Department of Health			Assessment group		
	Net cost (£)	*Net QALYs*	*ICER (£ per QALY)*	Net cost (£)	Net QALYs	ICER (£ per QALY)
All RSS DMTs	*31,838*	*0.943*	*33,748*	31,800	0.943	33,700
IFN β-1a 30µg IM once weekly (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1b 250 µg every other day (Betaferon)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44/22 µg SC three times a week (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg SC three times weekly (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6 DH ICERs using transparent NHS prices, incorporating AG modifications to the RSS model and with treatment waning

DMTs	Department of Health			Assessment group		
	Net cost (£)	*Net QALYs*	*ICER (£ per QALY)*	Net cost (£)	Net QALYs	ICER (£ per QALY)
All RSS DMTs	*35,845*	*0.812*	*44,151*	35,800	0.812	44,200
IFN β-1a 30µg IM once weekly (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1b 250 µg every other day (Betaferon)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44/22 µg SC three times a week (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg SC three times weekly (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AG comments: The results from the assessment group are in line with those provided by the Department of Health. As above, models included a weighted average of both doses of IFN β-1a SC three times a week (Rebif), 44 and 22 μg, weighted by their use in the RSS. We regard that any differences are likely due to rounding of the clinical effectiveness parameters, as the AG was only provided these to two decimal places.

Sensitivity analyses examining DMTs in aggregate, with assumptions as for the basic RSS model

The DH undertook scenario analyses around the implied hazard ratio and explored the impact of these on the base-case ICER. These assumptions along with the derived implied hazard ratios are presented in Table 7. The impact on the ICERs is shown in Table 8 and Table 9, without and with treatment waning, respectively. Based on the assumptions made in these new analyses, the implied hazard ratios appear to be reasonable in their magnitude relative to the 'base case' implied hazard ratio.

Table 7 DH Scenario analyses on the implied hazard ratio

Variant	Assumptions	Implied hazard ratio
Base-case	-	0.7913
C1a	Excluding data after patients have switched to a non-scheme DMT	0.7793
C1b	Excluding data after patients have switched to any other DMT	0.7666
C2	Missing data in the RSS imputed using the multilevel model to project forward from the available data for each patient	0.7928
C3a	Assumes that DMTs reduce the rate of backward transitions in the same proportion as for forward transitions	0.6003
C3b	Assumes that DMTs increase the rate of backward transitions in inverse proportion to the effect on forward transitions	0.8648
C4	Using transition matrices augmented to adjust for missing data in the BCMS dataset	0.7444
BCMS, British Columbia multiple sclerosis; DMT, disease modifying therapies; RSS, risk sharing scheme		

Table 8 Scenario analyses using the without treatment waning model

Variant	Department of Health			Assessment group		
	Net cost (£)	*Net QALYs*	*ICER (£ per QALY)*	Net cost (£)	Net QALYs	ICER (£ per QALY)
Base run	*31,684*	*1.047*	*30,262*	31,800	1.046	30,400
C1a	*29,998*	*1.113*	*26,956*	30,000	1.113	27,000
C1b	*28,197*	*1.183*	*23,830*	28,200	1.183	23,800
C2	*31,894*	*1.039*	*30,702*	31,900	1.039	30,700
C3a	*29,645*	*1.026*	*28,902*	29,600	1.026	28,900
C3b	*32,528*	*1.042*	*31,202*	32,500	1.042	31,200
C4	*23,095*	*1.309*	*17,643*	Not calculable by the AG		

Table 9 Scenario analyses using the with treatment waning model

Variant	Department of Health			Assessment group		
	Net cost (£)	*Net QALYs*	*ICER (£ per QALY)*	Net cost (£)	Net QALYs	ICER (£ per QALY)
Base run	*35,695*	*0.900*	*39,648*	35,900	0.899	39,900
C1a	*34,303*	*0.955*	*35,921*	34,300	0.955	35,900
C1b	*32,821*	*1.013*	*32,392*	32,800	1.013	32,400
C2	*35,868*	*0.893*	*40,144*	35,900	0.893	40,200
C3a	*34,327*	*0.875*	*39,239*	34,300	0.875	39,200
C3b	*36,345*	*0.898*	*40,464*	36,300	0.898	40,400
C4	*28,334*	*1.120*	*25,308*	Not calculable by the AG		

AG comment: These sensitivity analyses were undertaken using the RSS base case model not the AG base case model (in which, for example, we excluded carers' disutilities). Using the implied hazard ratios provided, the assessment group's results are in agreement with those submitted by the Department of Health. However, the assessment group was unable to replicate scenario analysis C4, which relates to transition matrices augmented for missing data in the BCMS dataset. We regard that any differences are likely due to rounding of the clinical effectiveness parameters, as the AG was only provided these to two decimal places.

Probabilistic sensitivity analysis: acceptance curve for the DH base case

The DH submitted a probabilistic sensitivity analysis for pooled DMTs using a pooled price of £8,000. AG attempts to replicate this PSA are found in Table 10 and Table 11.

Table 10 Probability of an ICER equal to or lower than threshold (without treatment waning), DH probabilistic sensitivity analyses

Threshold (cost per QALY)	Department of health	Assessment group
£20,000	*9.0%*	0.4%
£25,000	*28.0%*	8.8%
£30,000	*46.0%*	43.3%
£36,000*	*66.0%*	87.9%
£40,000	*79.7%*	98.4%
£45,000	*87.0%*	99.9%
£50,000	*93.0%*	100%

Table 11 Probability of an ICER equal to or lower than threshold (with treatment waning), DH probabilistic sensitivity analyses

Threshold (cost per QALY)	Department of Health	Assessment group
£20,000	*1.0*	0%
£25,000	*3.8*	0%
£30,000	*14.2*	1.5%
£36,000*	*37.4*	23%
£40,000	*52.8*	47.5%
£45,000	*71.1*	77.5%
£50,000	*82.0*	91.8%

Table 12 Department of Health and Assessment group deterministic and probabilistic results

Department of Health		Assessment group	
Deterministic results, cost per QALY	**Probabilistic results, cost per QALY**	**Deterministic results, cost per QALY**	**Probabilistic results, cost per QALY**
Using the without 'waning' model		**Using the without 'waning' model**	
£30,262	£31,200	£30,400	£30,600
Using the 'waning' model		**Using the 'waning' model**	
£39,648	£39,300	£39,900	£39,700

AG comment: The DH probabilistic sensitivity analyses only provide discrete values for the cost-effectiveness acceptability curves, and there appear to be some differences in the number of simulations undertaken at specific thresholds. We were unable to replicate the probabilities at each threshold. However, by interpolation, the approximate incremental cost-effectiveness ratios for the Department of Health models, along with those from the assessment group, have been reported in Table 12. These appear to match satisfactorily.

6 AG analyses for RRMS, including committee preferred assumptions, and sensitivity analyses using UK MS Society costs

In this section, we present new analyses for RRMS using the committee's preferred assumptions. To summarise, we understand the committee's preferred assumptions to consist of

- RSS data, supplemented by trial data (i.e. only using the AG network meta-analyses where no RSS data exist);
- including the assumption of treatment waning, (i.e. a 50% reduction in effectiveness after year 10 of treatment);
- the DH approach to estimating backward transitions in the EDSS health states;
- use of discontinuation rates as in the AG model, that is, 5% discontinue treatment every year;
- use of the current UK list prices for each drug; and
- including carers' disutilities.

We used RSS inputs for implied hazard ratio and annualised relapse rate as provided to the AG by the DH on 10 Jan 2017. These are documented in the table below (see Table 13). Analyses based on AG network meta-analyses were provided in Addendum 2a.

Table 13 Treatment effectiveness inputs from the DH provided on 10 Jan 2017

DMT	Implied hazard ratio	Annualised relapse rate ratio	Source
IFN β-1a 30µg IM once weekly (Avonex)	[redacted]	[redacted]	Obtained from the DH electronic document (NICE variants summary (ACIC)
IFN β-1b 250 µg every other day (Betaferon)	[redacted]	[redacted]	
Glatiramer acetate 20 mg SC once daily (Copaxone)	[redacted]	[redacted]	
IFN β-1a 22µg SC three times a week (Rebif)	[redacted]	[redacted]	
IFN β-1a 44µg SC three times a week (Rebif)	[redacted]	[redacted]	
Weighted average for Rebif	[redacted]	[redacted]	Derived from the treatment effectiveness from IFN β-1a 22µg and IFN β-1a 44µg SC three times a week (Rebif)
DH, Department of Health; DMT, disease modifying treatments; SC, subcutaneously			

Base case analysis

In Table 14 below, we present the base case results. These include a pooled price of £8,444 (the DH 'list price') and assume a pooled effect based on the RSS data. The ICER for the included DMTs as compared to best supportive care is approximately £44,300 per QALY gained. Note that this analysis excludes pegylated IFN β-1a 125 µg SC every two weeks (Plegridy) because this was not included in the RSS.

Table 14 Base case using committee's preferred assumptions

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
Disease modifying treatments	401,900	39,800	8.047	0.899	44,300
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Pairwise and incremental analyses for DMTs using individual DMTs and corresponding list prices

In Table 15 through Table 18, we present pairwise analyses for each drug included in the RSS against best supportive care. Please note that because RSS data for IFN β-1a three times a week (Rebif) were reported as a weighted average between the two doses (44 and 22 µg), we use an average of the transparent list prices weighted by the proportions of use of each dose in the RSS. This weighted average list price is £[redacted]. We remind readers that pegylated IFN β-1a 125 µg SC every two weeks (Plegridy) was not included in this appraisal and is thus not presented below. In Table 19, we present an incremental analysis for on-scheme DMTs using RSS data. Glatiramer acetate 20 mg SC once daily (Copaxone) dominates all other DMTs in this analysis and has an ICER of approximately [redacted] per QALY gained as compared to best supportive care.

Table 15 IFN β-1a 30µg IM once weekly (Avonex), using the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
IFN β-1a 30µg IM once weekly (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 16 IFN β-1b 250 µg every other day (Betaferon), using the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
IFN β-1b 250 µg every other day (Betaferon)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 17 Glatiramer acetate 20 mg SC once daily (Copaxone), using the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
Glatiramer acetate 20 mg SC once daily (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 18 IFN β-1a 44/22 µg SC three times a week (Rebif), using the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	
IFN β-1a 44/22 µg SC three times a week (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 19 Incremental analysis for RSS on-scheme DMTs, using the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	
Glatiramer acetate 20 mg SC once daily (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1b 250 µg every other day (Betaferon)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 30µg IM once weekly (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44/22 µg SC three times a week (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Pairwise analyses for DMTs using pooled RSS clinical parameters and individual drug list prices

In Table 20 through Table 24, we present pairwise analyses for each DMT included in this appraisal against best supportive care. We use the pooled RSS implied hazard ratio (0.7913) and relapse rate against each drug cost. This analysis is equivalent to assuming a class effect for all DMTs in this appraisal; that is, that effects are essentially interchangeable between DMTs. This reflects the clinical opinion expressed in the first appraisal committee meeting and was confirmed by our clinical advisors.

Because we assume a 'class effect' for all DMTs, we are able to include pegylated IFN β-1a 125 µg SC every two weeks (Plegridy) in this analysis. Please note again that because RSS data for IFN β-1a three times a week (Rebif) were reported as a weighted average between the two doses (44 and 22 µg), we use an average of the transparent list prices weighted by the proportions of use of each dose in the RSS. This weighted average list price is £[redacted].

Table 20 IFN β-1a 30µg IM once weekly (Avonex), using pooled RSS data and the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
IFN β-1a 30µg IM once weekly (Avonex)	402,400	40,300	8.047	0.899	44,800
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 21 IFN β-1b 250 µg every other day (Betaferon), using pooled RSS data and the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
IFN β-1b 250 µg every other day (Betaferon)	394,700	32,600	8.047	0.899	36,300
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 22 Glatiramer acetate 20 mg SC once daily (Copaxone), using pooled RSS data and the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
Glatiramer acetate 20 mg SC once daily (Copaxone)	386,600	24,500	8.047	0.899	27,300
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 23 IFN β-1a 44µg SC three times a week (Rebif), using the pooled RSS data and treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
IFN β-1a 44/22 µg SC three times a week (Rebif)	[redacted]	[redacted]	8.047	0.899	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 24 Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy), using pooled RSS data and the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)	402,400	40,300	8.047	0.899	44,800
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Pooled beta interferons and glatiramer using RSS data and list prices

In this analysis, we considered the pooled RSS data for on-scheme beta-interferons and the RSS data for glatiramer separately. We took the weighted average of the RSS list prices for on-scheme beta-interferons, weighting by their use in the RSS [redacted]). The results of this analysis are presented in Table 25 and reflect that glatiramer acetate dominates the pooled on-scheme beta-interferons.

Table 25 Scenario analysis results comparing beta interferons, glatiramer acetate 20 mg SC once daily on list prices using the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
Glatiramer acetate 20 mg SC once daily (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta interferons	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Parameter uncertainty analysis: pooled DMTs using the committee's preferred assumptions

We varied the hazard ratio for disability progression, the rate ratio for annualised relapse rates, cost of disease modifying treatments, and the annual discontinuation rate by ±10% for the base case using the committee's preferred assumptions.

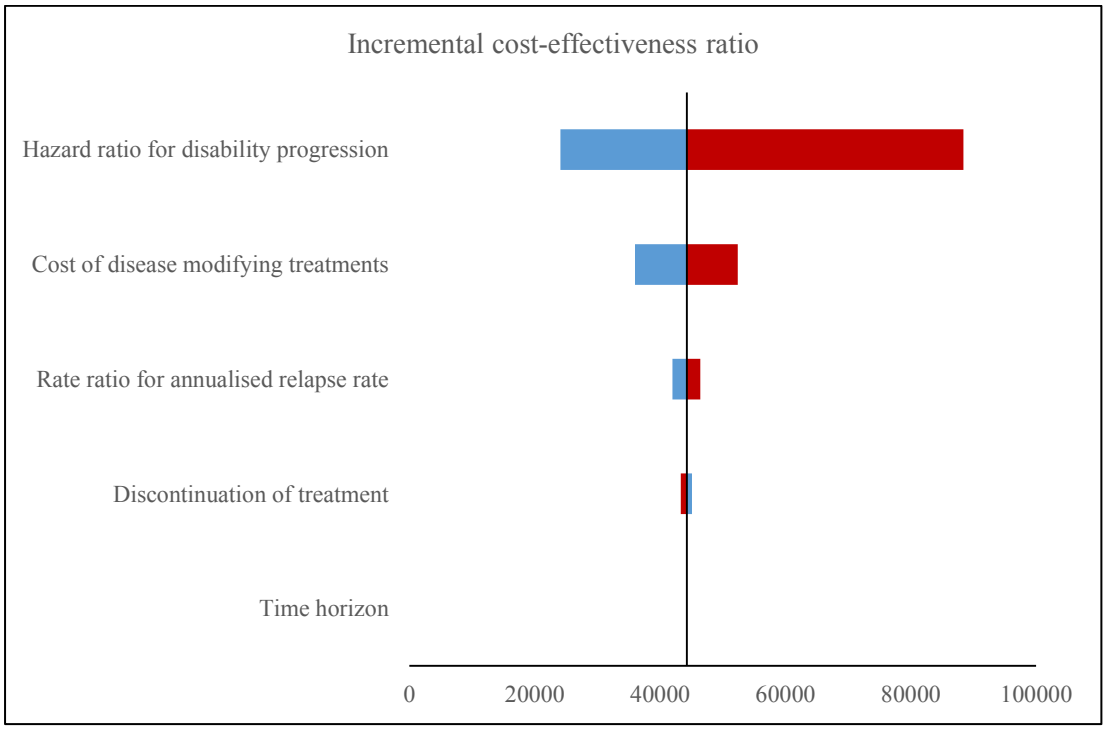

Figure 1 Tornado diagram for DMTs vs. best supportive care based on the treatment waning model

Figure 1 shows the impact on the ICER by varying model input parameters. Results from the tornado diagrams showed that the hazard ratio for disability progression continued to have the greatest impact on the incremental cost-effectiveness ratio.

Probabilistic sensitivity analysis: pooled DMTs using the committee's preferred assumptions

We used 1000 Monte Carlo simulations in a probabilistic sensitivity analysis accounting for the implied hazard ratio, rate ratio for annualised relapse rate and utilities. Results from the probabilistic sensitivity analysis are in line with the results from the deterministic analysis based on incremental cost per QALY (see Table 26). Figure 2 and Figure 3 show the scatterplot and the cost-effectiveness acceptability curve for DMTs compared to best supportive care, respectively. For the 1000 Monte Carlo simulations the scatterplot shows some uncertainty in the incremental costs and incremental QALYs (Figure 2). The cost-effectiveness acceptability curve (CEAC) shows that at a willingness-to-pay threshold of £30,000 per QALY, the probability of DMTs being cost-effective when compared to best supportive care is 0.001.

Table 26 Probabilistic sensitivity analysis using the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	364,600	-	7.16	-	-
Disease modifying treatment	404,100	39,500	8.05	0.89	44,400
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

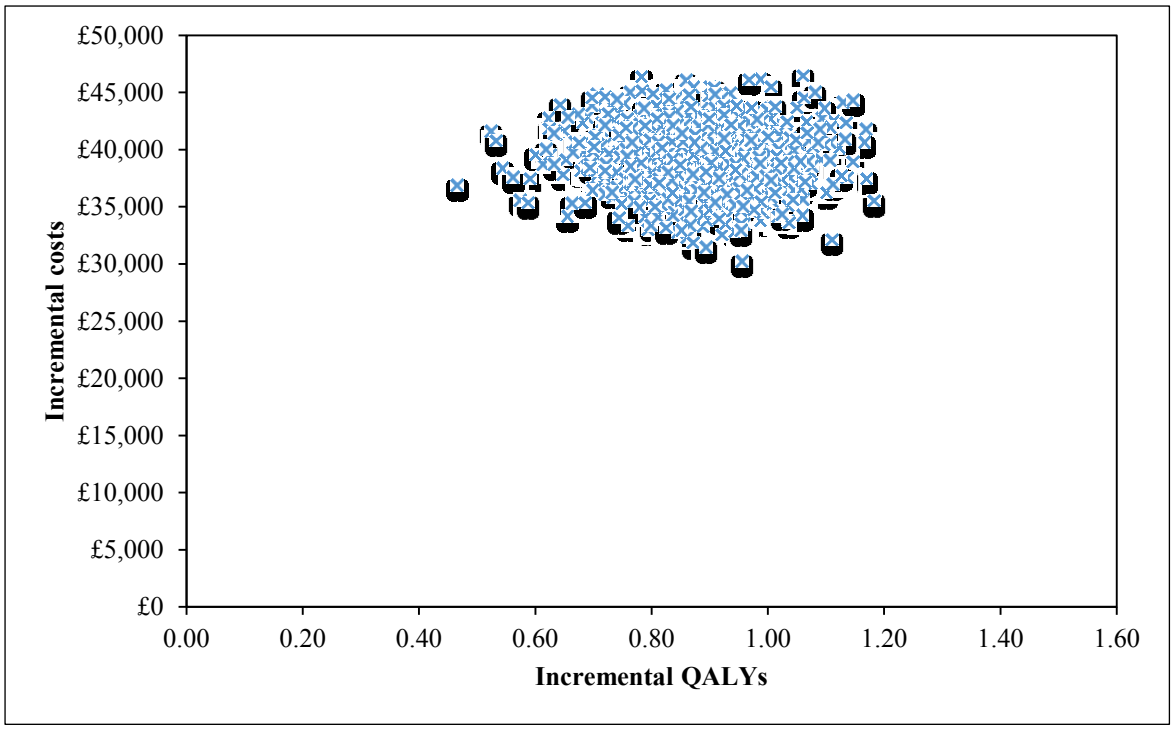

Figure 2 Cost-effectiveness plane, probabilistic sensitivity analysis conducted using the treatment waning model

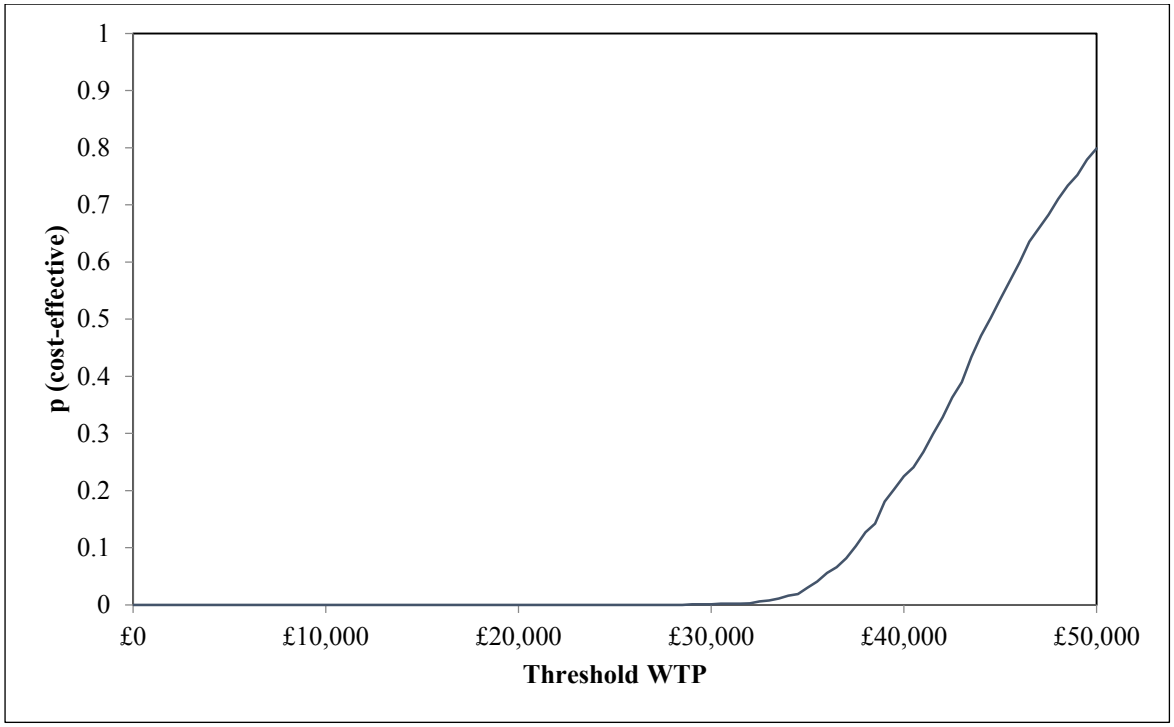

Figure 3 Cost-effectiveness acceptability curve, probabilistic sensitivity analysis conducted using the treatment waning model

Sensitivity analyses using UK MS Survey health state costs

The AG re-estimated the deterministic models presented above using costs derived from the UK MS Survey undertaken in 2005/6.[5] These costs have been used in recent MS-related appraisals and are reproduced below in Table 27 showing prices inflated to 2014/5 levels.[6]

Table 27 UK MS Survey health state management costs

EDSS	2005/06 prices	2014/15 prices
0	638	937
1	927	974
2	883	714
3	2758	3906
4	1756	1892
5	2543	3210
6	3146	4285
7	7384	11,279
8	17,370	27,472
9	16,307	21,982
0	0	0

The analysis for pooled DMTs is presented below (see Table 28). As compared to the base case model, the ICER in this model is considerably higher at £59,800 per QALY gained.

Table 28 Sensitivity analysis results based on committee's preferred assumptions, using UK MS survey management costs and the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	225,700	-	7.148	-	-
Disease modifying treatment	279,500	53,800	8.047	0.899	59,800
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

The analyses for on-scheme DMTs using DMT-specific estimates of implied hazard ratio and relapse rate and individual DMT costs are presented below (see Table 29 through Table 32). As expected, ICERs across all models are higher compared to models using the AG estimates of health state costs.

Table 29 IFN β-1a 30µg IM once weekly (Avonex), using UK MS survey management costs and the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	225,700	-	7.148	-	-
IFN β-1a 30µg IM once weekly (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 30 IFN β-1b 250 µg every other day (Betaferon), using UK MS survey management costs and the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	225,700	-	7.148	-	-
IFN β-1b 250 µg every other day (Betaferon)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 31 Glatiramer acetate 20 mg SC once daily (Copaxone), using UK MS survey management costs and the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	225,700	-	7.148	-	-
Glatiramer acetate 20 mg SC once daily (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 32 IFN β-1a 44/22 µg SC three times a week (Rebif), using UK MS survey management costs and the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	225,700	-	7.148	-	-
IFN β-1a 44/22 µg SC three times a week (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

The incremental analysis, as presented below (see Table 33), suggests that while glatiramer acetate 20 mg SC once daily (Copaxone) still dominates all other strategies, it is no longer cost effective with an ICER of [redacted] per QALY gained as compared to best supportive care.

Table 33 Incremental analysis, DMT-specific RSS estimates using UK MS survey management costs and the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	225,700	-	7.148	-	-
Glatiramer acetate 20 mg SC once daily (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1b 250 µg every other day (Betaferon)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 30µg IM once weekly (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44µg SC three times a week (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Next, the pairwise analyses for DMTs using pooled RSS estimates of implied hazard ratio and relapse rate against individual drug costs are presented below (see Table 34 through Table 38). As expected, ICERs across all models are higher compared to models using the AG estimates of health state costs.

Table 34 IFN β-1a 30µg IM once weekly (Avonex), using pooled RSS estimates, the treatment waning model and UK MS survey management costs

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	225,700	-	7.148	-	-
IFN β-1a 30µg IM once weekly (Avonex)	280,000	54,300	8.047	0.899	60,400
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 35 IFN β-1b 250 µg every other day (Betaferon), using pooled RSS estimates, the treatment waning model and UK MS survey management costs

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	225,700	-	7.148	-	-
IFN β-1b 250 µg every other day (Betaferon)	269,100	43,400	8.047	0.899	48,300
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 36 Glatiramer acetate 20 mg SC once daily (Copaxone), using pooled RSS estimates, the treatment waning model and UK MS survey management costs

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	225,700	-	7.148	-	-
Glatiramer acetate 20 mg SC once daily (Copaxone)	264,200	38,500	8.047	0.899	42,800
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 37 Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy), using pooled RSS estimates, the treatment waning model and UK MS survey management costs

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	225,700	-	7.148	-	-
Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)	280,000	54,300	8.047	0.899	60,400
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 38 IFN β-1a 44/22 µg SC three times a week (Rebif), using pooled RSS estimates, the treatment waning model and UK MS survey management costs

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	225,700	-	7.148	-	-
IFN β-1a 44/22 µg SC three times a week (Rebif)	[redacted]	[redacted]	8.047	0.899	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Finally, comparison of best supportive care, glatiramer acetate 20 mg SC once daily (Copaxone) and pooled on-scheme beta-interferons continues to show that glatiramer acetate 20 mg SC once daily (Copaxone) dominates the pooled beta-interferons (see Table 39).

Table 39 Scenario analysis results comparing beta interferons, glatiramer acetate 20 mg SC once daily and using the treatment waning model and UK MS survey management costs

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	225,700	-	7.148	-	-
Glatiramer acetate 20 mg SC once daily (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta interferons	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

7 AG analyses for CIS, including committee preferred assumptions, and sensitivity analyses using UK MS Society costs

The CIS model developed by the AG includes two stages: treatment for people with CIS up to progression to RRMS, and disease progression whilst in the RRMS health state. Information on the treatment effectiveness for each DMT in delaying progression to RRMS, and for DMTs collectively, was obtained from the assessment group's (AG's) network meta-analysis; whilst the pooled treatment effectiveness for DMTs in delaying progression in RRMS was based on information from the RSS.

In the CIS and RRMS phases of the model, we used the list prices obtained from the BNF, 2015[7] for each DMT and the weighted average cost of DMTs (£8444), respectively. Because only the 44 µg dose of IFN β-1a SC three times a week (Rebif) is included in the network meta-analyses, we used the list price for this dose alone (see Table 40).

Table 40 Prices used in the CIS model

DMTs	List prices (£, 2015)	Sources/notes
Pooled DMTs	8444	Obtained from the DH, discussed above
IFN β-1a 30µg IM once weekly (Avonex)	8502	British National Formulary (BNF), 2015[7]
IFN β-1b 250 µg every other day (Betaferon)	7264	
Glatiramer acetate 20 mg SC once daily (Copaxone)	6704	
IFN β-1a **44 µg** SC three times a week (Rebif)	10,572	
CIS, clinically isolated syndrome; DMT, disease modifying treatment; RRMS, relapsing remitting multiple sclerosis; SC, subcutaneously		

In the RRMS stage of the model, we used the committee's preferences as stated in the previous section. We 'started the clock' on the treatment waning assumption on conversion to RRMS.

As part of these analyses, we used two strategies as comparators: best supportive care for both CIS and RRMS, and best supportive care for CIS followed by DMTs for RRMS. We tested a pooled effect for DMTs derived from the AG network meta-analysis of DMTs for CIS. We also tested each DMT separately and incrementally.

Pooled DMTs for CIS

The pooled effect across all trials for DMTs in CIS was HR=0.514 (95% CI 0.436, 0.608). Table 41 reports the results using the treatment waning model. Using the time-varying treatment effects model, the strategy of using pooled DMTs for treatment of CIS and RRMS continued to extendedly dominate

best supportive care for CIS followed by DMTs for RRMS, with an ICER of approximately £21,200 per QALY when compared to best supportive care for CIS and RRMS.

Table 41 Base case results for CIS, pooled DMTs, including committee's assumptions and the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	159,500	-	12.44	-	-
BSC for CIS and DMTs for RRMS	180,100	20,600	12.86	0.42	Extendedly dominated
DMTs for CIS and RRMS	234,300	74,800	15.97	3.53	21,200

Individual DMTs for CIS

Table 42 through Table 45 present the pairwise analyses for

- each DMT against BSC for both CIS and RRMS, and
- against BSC for CIS and DMTs as a group for RRMS.

Pairwise analyses comparing

- each DMT licensed for CIS against BSC in CIS and RRMS, and
- BSC in CIS followed by DMTs for RRMS

showed that all drugs were cost-effective compared to BSC in CIS and RRMS, with BSC followed by DMTs extendedly dominated in all analyses. These analyses further showed that glatiramer acetate 20 mg SC once daily (Copaxone) had the lowest ICER when compared to BSC in CIS and RRMS. This was confirmed in the incremental analysis presented in Table 46, in which glatiramer acetate 20 mg SC once daily (Copaxone) dominated all other strategies.

Table 42 IFN β-1a 30µg IM once weekly (Avonex) for CIS, including committee's assumptions and using the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	159,500	-	12.44	-	-
BSC for CIS and DMTs for RRMS	180,100	20,600	12.86	0.42	Extendedly dominated
IFN β-1a 30µg IM once weekly (Avonex) for CIS and DMTs for RRMS	268,300	108,800	18.06	5.62	19,400

Table 43 IFN β-1b 250 µg every other day (Betaferon) for CIS, including committee's assumptions and using the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	159,500	-	12.44	-	-
BSC for CIS and DMTs for RRMS	180,100	20,600	12.86	0.42	Extendedly dominated
IFN β-1b 250 µg every other day (Betaferon) for CIS and DMTs for RRMS	229,000	69,500	16.46	4.02	17,300

Table 44 Glatiramer acetate 20 mg SC once daily (Copaxone) for CIS, including committee's assumptions and using the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	159,500	-	12.44	-	-
BSC for CIS and DMTs for RRMS	180,100	20,600	12.86	0.42	Extendedly dominated
Glatiramer acetate 20 mg SC once daily (Copaxone) for CIS and DMTs for RRMS	251,500	92,000	18.21	5.77	15,900

Table 45 IFN β-1a 44µg SC three times a week (Rebif) for CIS, including committee's assumptions and using the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	159,500	-	12.44	-	-
BSC for CIS and DMTs for RRMS	180,100	20,600	12.86	0.42	Extendedly dominated
IFN β-1a 44µg SC three times a week (Rebif) for CIS and DMTs for RRMS	274,200	114,700	17.17	4.73	24,200

Table 46 Incremental analysis of DMTs for CIS, including committee's assumptions and using the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	159,500	-	12.44	-	-
BSC for CIS and DMTs for RRMS	180,100	20,600	12.86	0.42	Extendedly dominated
IFN β-1b 250 µg every other day (Betaferon) for CIS and DMTs for RRMS	229,000	69,500	16.46	4.02	Extendedly dominated
Glatiramer acetate 20 mg SC once daily (Copaxone) for CIS and DMTs for RRMS	251,500	92,000	18.21	5.77	15,900
IFN β-1a 30µg IM once weekly (Avonex) for CIS and DMTs for RRMS	268,300	16,800	18.06	-0.15	Dominated
IFN β-1a 44µg SC three times a week (Rebif) for CIS and DMTs for RRMS	274,200	22,700	17.17	-1.04	Dominated

These analyses demonstrate enhanced cost effectiveness of the DMTs in the management of CIS and RRMS as compared to their cost effectiveness in the management of RRMS alone. We account for this difference mainly because of the use of the AG network meta-analyses as the only source of information for estimating the effectiveness of the DMTs in CIS. The AG network meta-analyses, whilst based on rigorous systematic review, nevertheless use recent RCT evidence which involves short term follow-up. We consider that the estimates of effectiveness which it generates may overestimate the benefits of DMTs. This is the reason for our use of RSS values throughout our analyses wherever these are available.

Sensitivity analyses using UK MS Survey health state costs

As for RRMS analyses, we present analyses for CIS including UK MS Survey health state costs (see Table 47 through Table 51). These costs were applied upon conversion to RRMS. The pattern of results echoes the results presented above, but as expected ICERs are higher in all analyses.

Table 47 Base case results for CIS, using UK MS Survey costs and the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	102,100	-	12.44	-	-
BSC for CIS and DMTs for RRMS	129,700	27,600	12.86	0.42	Extendedly dominated
DMTs for CIS and RRMS	191,300	89,200	15.97	3.53	25,300

Table 48 IFN β-1a 30µg IM once weekly (Avonex) results for CIS, using UK MS Survey costs and the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	102,100	-	12.44	-	-
BSC for CIS and DMTs for RRMS	129,700	27,600	12.86	0.42	Extendedly dominated
IFN β-1a 30µg IM once weekly (Avonex) for CIS and DMTs for RRMS	223,000	102,900	18.06	5.62	21,500

Table 49 IFN β-1b 250 µg every other day (Betaferon) results for CIS, using UK MS Survey costs and the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	102,100	-	12.44	-	-
BSC for CIS and DMTs for RRMS	129,700	27,600	12.86	0.42	Extendedly dominated
IFN β-1b 250 µg every other day (Betaferon) for CIS and DMTs for RRMS	185,900	83,800	16.46	4.02	20,800

Table 50 Glatiramer acetate 20 mg SC once daily (Copaxone) results for CIS, using UK MS Survey costs and the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	102,100	-	12.44	-	-
BSC for CIS and DMTs for RRMS	129,700	27,600	12.86	0.42	Extendedly dominated
Glatiramer acetate 20 mg SC once daily (Copaxone) for CIS and DMTs for RRMS	204,900	102,800	18.21	5.77	17,800

Table 51 IFN β-1a 44µg SC three times a week (Rebif) results for CIS, using UK MS Survey costs and the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	102,100	-	12.44	-	-
BSC for CIS and DMTs for RRMS	129,700	27,600	12.86	0.42	Extendedly dominated
IFN β-1a 44µg SC three times a week (Rebif) for CIS and DMTs for RRMS	231,000	128,900	17.17	4.73	27,300

8 Scenario analyses documenting the relevance of different relapse management costs in RRMS

Following the first appraisal committee meeting, the large variation in costs of relapse management was raised as a potential issue in this appraisal. A table of relapse costs used in different appraisals is provided below (see Table 52). This table is substantially based on a similar table produced as part of the appraisal of dimethyl fumarate for RRMS, by McDaid and colleagues at the University of York in 2013.[8]

Table 52 Alternative sources for costs of managing relapses

Reference	Relapse cost estimate	Cost year	Relapse cost estimate (2016 prices)	Data source
MS MTA[9]	4263	2016	4263	ScHARR analysis
Natalizumab (TA127)[10]	228	2005	292	MS survey
Tyas et al.[11]	1623	2007	1930	MS survey
Fingolimod (TA254)[12]	3039	2010	3360	NHS reference costs
Alemtuzumab (TA312)[13]	1909	2013	1973	NHS reference costs

The AG was unable to account for the differences in relapse management costs, as these would not have arisen by inflation alone. It notes that this difficulty in evaluating the provenance of different relapse costs is not unique—the ERG evaluating dimethyl fumarate noted that it was impossible to fully account for the differences of costs, even arising from the same data source. We obtained our estimate of relapse costs by inflating the estimate from the original ScHARR model, which formed the basis for the RSS model.

To evaluate the degree to which relapse costs influence the cost effectiveness of the DMTs in this appraisal, we present several sensitivity analyses. They collectively suggest that differences in relapse cost—even large differences—do not drive the ICER and are relatively lacking in importance when compared to the other parameters in this model. In Table 53 through Table 57, we present the base case using the committee's preferred assumptions and different relapse cost. In addition, we present a tornado diagram in Figure 4 which shows the impact of varying key parameters by 50% in the base case using the committee's preferred assumptions. It is clear from these analyses and the tornado diagram that the ICER is not driven by the cost of relapse management.

Table 53 Scenario analysis results based on committee's preferred assumptions, using relapse management costs from current MS MTA

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
Disease modifying treatments	401,900	39,800	8.047	0.899	44,300
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 54 Scenario analysis results based on committee's preferred assumptions, using relapse management costs from Natalizumab submission (TA127)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	323,500	-	7.148	-	-
Disease modifying treatment	366,500	43,000	8.047	0.899	47,800
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 55 Scenario analysis results based on committee's preferred assumptions, using relapse management costs from Tyas et al.

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	339,400	-	7.148	-	
Disease modifying treatment	381,100	41,700	8.047	0.899	46,400
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 56 Scenario analysis results based on committee's preferred assumptions, using relapse management costs from Fingolimod submission

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	353,300		7.148	-	
Disease modifying treatment	393,800	40,500	8.047	0.899	45,100
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 57 Scenario analysis results based on committee's preferred assumptions, using relapse management costs from Alemtuzumab submission

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	339,900	-	7.148	-	-
Disease modifying treatment	381,400	41,500	8.047	0.899	46,200
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

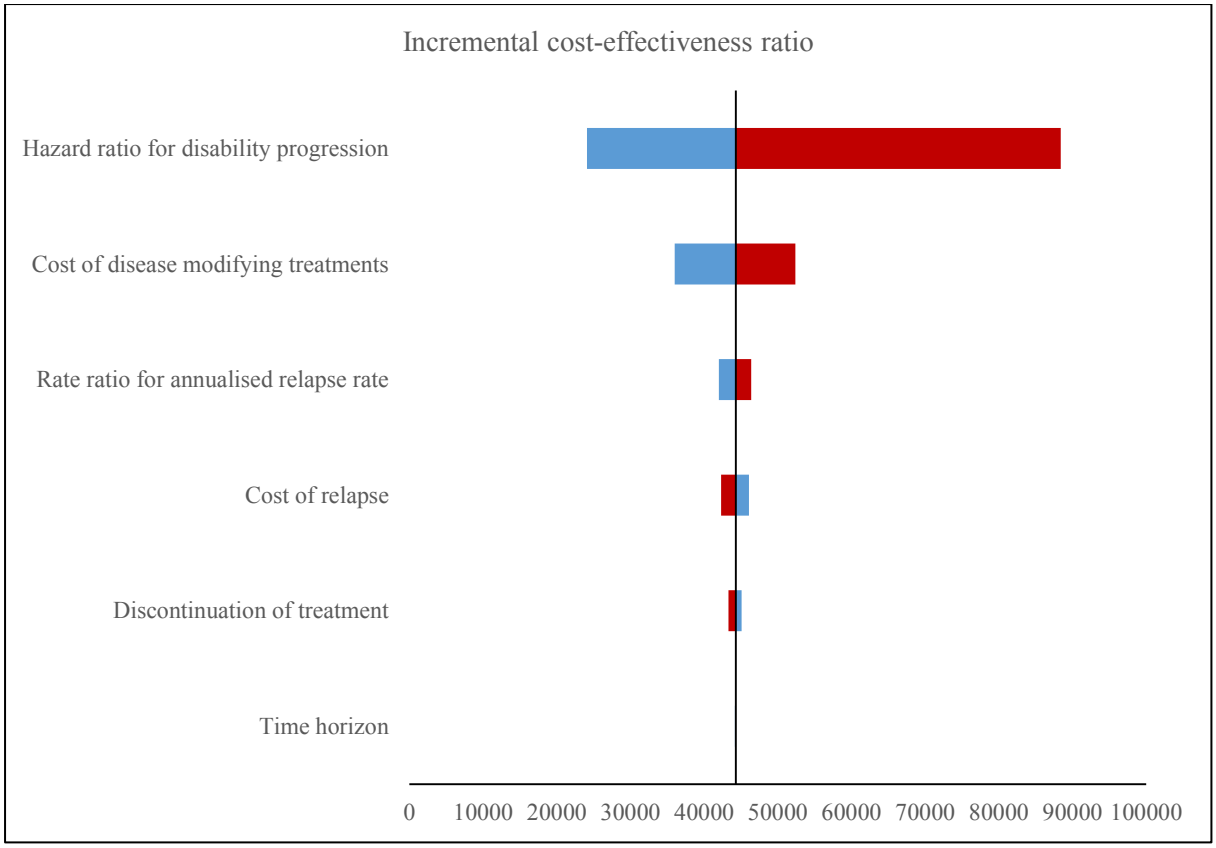

Figure 4 Tornado diagram for DMTs versus best supportive care based on the treatment waning model

9 Account of issues with comparing pegylated IFN β-1a (Plegridy) with other drugs in RSS

Modelling the cost effectiveness of pegylated IFN β-1a 125 µg SC every two weeks (Plegridy) alongside the DMTs included in the RSS poses several challenges. In incremental analyses provided in the original report and in subsequent addenda, pegylated IFN β-1a (Plegridy) was frequently a dominant strategy. However, these analyses relied on clinical effectiveness parameters estimated as part of the AG network meta-analyses. Both the committee and the AG considered that the RSS data were likely to be preferable. The AG considered that the RSS data provided a more convincing base case than data from the network meta-analyses because of the much longer followup afforded by the RSS data even though the RSS data were based on an observational study design with historical comparator data. There are several options, for attempting to compare the cost-effectiveness of pegylated IFN β-1a alongside the other DMTs included in the RSS and we discuss the benefits and drawbacks of each below. We consider that, given the committee's preferred assumptions, ascribing the pooled class effect from DMTs to pegylated IFN β-1a 125 µg SC every two weeks (Plegridy) may be the most sensible approach.

Accepting an analysis based on the AG network meta-analyses

A cost effectiveness analysis using clinical effectiveness parameters based on the AG NMA has the principal benefit of providing data for all DMTs from randomised controlled trials. However, as mentioned above we consider that this analysis reflects the weakness of the body of clinical trials both as a whole and in relation to individual drugs. As noted in our original report, trials were primarily short term and industry sponsored. In addition, the evidence base for pegylated IFN β-1a was particularly sparse and consisted of one relatively short-term trial (ADVANCE 2014)[14] linked to the evidence networks for the different clinical outcomes by placebo alone.

Using a rescaling-based method to approximate an 'RSS-equivalent' implied hazard ratio and relapse rate for pegylated IFN β-1a 125 µg (Plegridy)

Hypothetically, the AG could rescale the estimates of time to progression in the AG network meta-analyses to relate the effectiveness of pegylated IFN β-1a (Plegridy) from hazard ratio to implied hazard ratio. While this method has the benefit of providing an approximation of the implied hazard ratio for pegylated IFN β-1a (Plegridy), it is not without major problems.

First, any rescaling would be susceptible to the choice of outcome measure, each of which carries distinct problems. Time to progression is measured in trials of DMTs for MS using confirmation at three months and confirmation at six months. The AG referred to these outcomes in the main report as TTP3 and TTP6 respectively. The AG preferred TTP3 in the economic models based on the AG network meta-analyses, because the network for TTP3 was better populated with trials than the network for TTP6, and the network meta-analysis for TTP6 resulted in comparisons between DMTs and placebo based on indirect evidence alone that were clinically unrealistic. However, previous appraisal committees have preferred TTP6 in appraisals of DMTs for MS because TTP6 may better approximate 'true' disability progression. As noted in the AG report, findings from the network meta-analyses for TTP3 and TTP6 did not produce similar 'rankings' of drugs. Thus, any rescaling would be sensitive to choice of outcome measure.

Second, and as noted above, the network meta-analyses including pegylated IFN β-1a (Plegridy) linked to the evidence networks by placebo alone on the basis of one trial. This provides an especially weak basis for rescaling as compared to the evidence base for the other drugs included in this appraisal.

Third, the AG considered that data from the RSS provided a stronger evidence base for the real-world effectiveness of DMTs as compared to the clinical trials, while acknowledging that the RSS data, which arise from an observational cohort, are susceptible to selection and information biases. Using a rescaling method could lead to an estimate for pegylated IFN β-1a (Plegridy) that 'synthesises' these

biases, leading to an estimate of the implied hazard ratio for pegylated IFN β-1a (Plegridy) that might be uniquely biased as compared to the estimates for other DMTs.

Using a pooled class effect for DMTs and individual drug costs

Another approach is to assume a pooled class effect for the DMTs as estimated in the RSS and assign this value to all DMTs, with costs from individual DMTs. We present these analyses above, under subheading 'Pairwise analyses for DMTs using pooled RSS clinical parameters and individual drug list prices'. This has several benefits. First, and principally, it reflects the clinical opinion expressed in AC1 and confirmed by the AG clinical advisors that the DMTs considered in this appraisal could be considered as part of a class of drugs, with exchangeable effects. Second, it provides a transparent basis for assigning effectiveness parameters to pegylated IFN β-1a (Plegridy), consistent with the appraisal committee's preferred data source, the RSS. Third, an analysis based on the pooled implied hazard ratio from the RSS includes considerably more information in person-years than the combined trials from the relevant outcome networks in the network meta-analyses. The principal drawback of this method is that any potential benefit of pegylated IFN β-1a (Plegridy) relative to other DMTs in this appraisal is not included in this analysis. However, the network meta-analyses undertaken by the AG did not suggest that pegylated IFN β-1a (Plegridy) was superior to other DMTs in respect of annualised relapse rate or either outcome relating to time to disability progression.

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APPENDIX: Changes to our original report taking account of DH errors in price reporting

Since submission of our original report in August 2016, we have updated several analyses due to updates in clinical parameters provided by the DH. We append here the updated analyses, mapped against the tables in our original report.

Results of the RRMS cost-effectiveness analysis

We present analyses below relating to the base run model **as defined by the AG in the original report**; that is, excluding carers' disutilities and without treatment waning. We present the modified analyses accounting for carers' disutilities and treatment waning at the end of this report. Analyses for pooled DMTs used a pooled price of £8,000.

Base Case

In Table 1, we present the findings from our base case analysis. The results showed that at a 50-year time horizon the DMT strategy was more costly and more effective than best supportive care. The expected mean costs per person for the disease modifying treatment strategy were approximately £31,900 more costly than the best supportive care strategy and produced 0.943 more QALYs with an ICER of approximately £33,800 per QALY.

Table 1: Base case results based cost per QALY

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
Disease modifying treatments	394,000	31,900	9.607	0.943	33,800
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

SA 1: Pooled on-scheme DMTs from assessment group review

We used two key estimates of treatment effectiveness from our clinical effectiveness review: the aggregated hazard ratio for disability progression confirmed at 3 months and the aggregated annualised relapse rate.

In Table 2, the results are presented in terms of cost per QALY. The results show that disease modifying treatment strategy was more costly and more effective than best supportive care alone. The disease modifying treatment strategy was approximately £23,300 more costly than best supportive care and produced 1.822 more QALYs, which equated to an ICER of approximately £12,800 per QALY. This indicates that for every additional QALY from DMTs there is an incremental cost of £12,800.

Table 2: Cost per QALY, SA 1

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
Disease modifying treatments	385,400	23,300	10.486	1.822	12,800
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

SA 2a Individual drugs from AG review, progression confirmed at 3 months (preferred analysis)

In this model, we used the hazard ratios (DMT vs. placebo) for disability progression confirmed at three months (**Error! Reference source not found.**) and annualised relapse rates (**Error! Reference source not found.**) derived from our clinical effectiveness review applied to the individual DMTs.

Results from this sensitivity analysis (see Table 3) show that best supportive care was the least expensive strategy and IFN β-1a 30µg IM once weekly (Avonex) the most expensive. In terms of QALYs, best supportive care is expected to result in the least QALYs (8.664) and IFN β-1a 125 µg SC every two weeks (Plegridy) expected to yield the most QALYs (11.223). IFN β-1a 125 µg (Plegridy) dominated all other disease modifying treatment strategies being less costly and more effective. When compared to best supportive care, IFN β-1a 125 µg (Plegridy) was approximately £17,800 more costly and was more effective by expected mean gains of 2.559 QALYs, with an ICER of £7000 per QALY.

Table 3: Cost per QALY, SA 2a (assessment group estimates, progression confirmed at 3 months)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
IFN β-1a 125µg (Plegridy)	379,900	17,800	11.223	2.559	7000
Glatiramer acetate 20mg (Copaxone)	381,400	1500	10.012	-1.211	Dominated
IFN β-1b 250µg every other day (Betaferon/Extavia)	393,400	13,500	9.934	-1.289	Dominated
INF β-1a 44µg SC (Rebif)	404,800	24,900	10.867	-0.356	Dominated
IFNβ-1a 30µg IM (Avonex)	406,400	26,500	10.348	-0.875	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

SA 2b: Individual drugs from AG review, progression confirmed at 6 months

In this sensitivity analysis, we used hazard ratios for disability progression confirmed at 6 months derived from our clinical effectiveness review, findings showed that IFN β-1a 125 µg SC every two weeks (Plegridy) was the least costly and most effective treatment strategy, dominating other treatment strategies included in this analysis (see Table 4). We did not include IFN β-1b 250µg every

other day (Betaferon/Extavia) in this analysis as its value for progression confirmed at 6 months was a) extreme, b) derived from indirect evidence, and c) driven by one open-label trial using an imputed hazard ratio.

Table 4: Cost per QALY, SA 2b (assessment group estimates, disability progression confirmed at 6 months)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
IFN β-1a 125 µg SC every two weeks (Plegridy)	347,000	-	12.583	-	-
Best supportive care	362,100	15,100	8.664	-3.919	Dominated
IFN β-1a 44 µg SC three times a week (Rebif)	377,600	30,600	12.041	-0.542	Dominated
Glatiramer acetate 20 mg SC daily (Copaxone)	391,800	44,800	9.650	-2.933	Dominated
IFN β-1a 30 µg IM once weekly (Avonex)	397,200	50,200	10.717	-1.866	Dominated
BSC, best supportive care; IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

SA 3: Hazard ratios from company submissions

When we used the estimates for treatment effectiveness (annualised relapse rate and disability progression) reported by each company, results from this sensitivity analysis showed that best supportive care was the least expensive strategy and [redacted] When compared to best supportive care, IFN β-1a 125 µg (Plegridy) demonstrated an ICER of [redacted] per QALY.

Table 5: Cost per QALY, SA 3 (company estimates of effectiveness)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
IFN β-1a 125 µg SC every two weeks (Plegridy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 40 mg SC three times weekly (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 30µg IM once weekly (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44µg SC three times a week (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

SA 4: Time horizon changed from 50 years to 20 and 30 years

Table 6 and Table 7 show the results based on a 20-year and 30-year time horizon, respectively. These results showed that the glatiramer acetate treatment strategy is extendedly dominated by IFN β-1a 125 µg (Plegridy) in both analyses. Additionally, IFN β-1a 125 µg (Plegridy) dominated both IFN β-1a 30 µg IM (Avonex) and IFN β-1a 44µg SC (Rebif) treatment strategies. Excluding all dominated strategies, IFN β-1a 125 µg (Plegridy) when compared to best supportive care had an ICER of approximately £21,200 and £10,600 per QALY for the 20-year and 30-year time horizon, respectively.

Table 6: Cost per QALY, SA 4 (time horizon changed to 20 years)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	196,900	-	6.644	-	-
Glatiramer acetate 20mg (Copaxone)	220,900	24,000	7.436	0.792	Extendedly dominated
IFNβ-1a 125µg (Plegridy)	225,800	28,900	8.007	1.363	21,200
IFNβ-1a 30µg IM (Avonex)	242,900	17,100	7.570	-0.437	Dominated
INFβ-1a 44µg SC (Rebif)	245,200	19,400	7.882	-0.125	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous					

Table 7: Cost per QALY, SA 4 (time horizon changed to 30 years)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	279,400	-	7.774	-	-
Glatiramer acetate 20mg (Copaxone)	299,400	20,000	8.874	1.1	Extendedly dominated
IFNβ-1a 125µg (Plegridy)	300,400	21000	9.756	1.982	10,600
INFβ-1a 44µg SC (Rebif)	322,900	22500	9.532	-0.224	Dominated
IFNβ-1a 30µg IM (Avonex)	323,300	22,900	9.103	-0.653	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous					

SA 5: Parameter uncertainty analysis

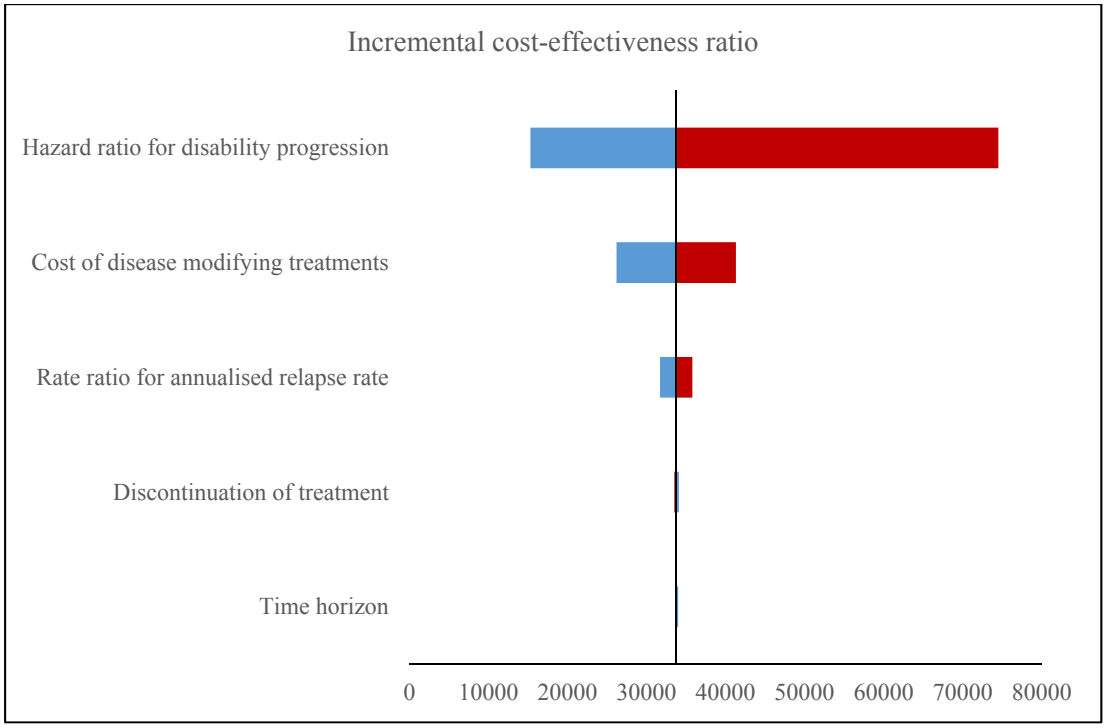


Figure 1 shows a graphical representation (also known as a tornado diagram) of the impact **on the base case** of varying key model input parameters. In this analysis, we varied the hazard ratio for disability progression, the rate ratio for annualised relapse rates, cost of disease modifying treatments, and the annual discontinuation rate by ±10%. Additionally, we assessed the impact of the base case results by varying the model time horizon by ±10%. The results show that changes to the hazard ratio for disability progression have the greatest impact on the cost-effectiveness results. A decrease in the treatment effect (increase in the hazard ratio) by 10% resulted in an ICER of approximately £74,500 per QALY gained. An increase in the treatment effect (decrease in the hazard ratio) by 10% resulted in an ICER of approximately £15,300 per QALY gained. The model remained robust to changes to the treatment discontinuation rate and the model time horizon.

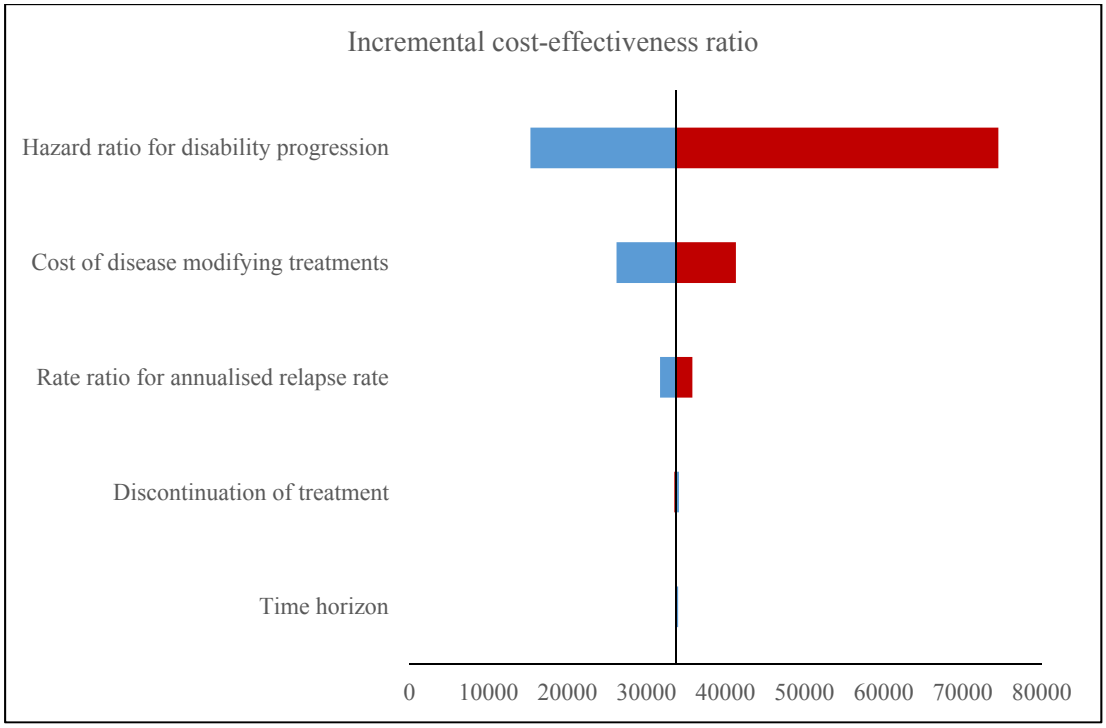
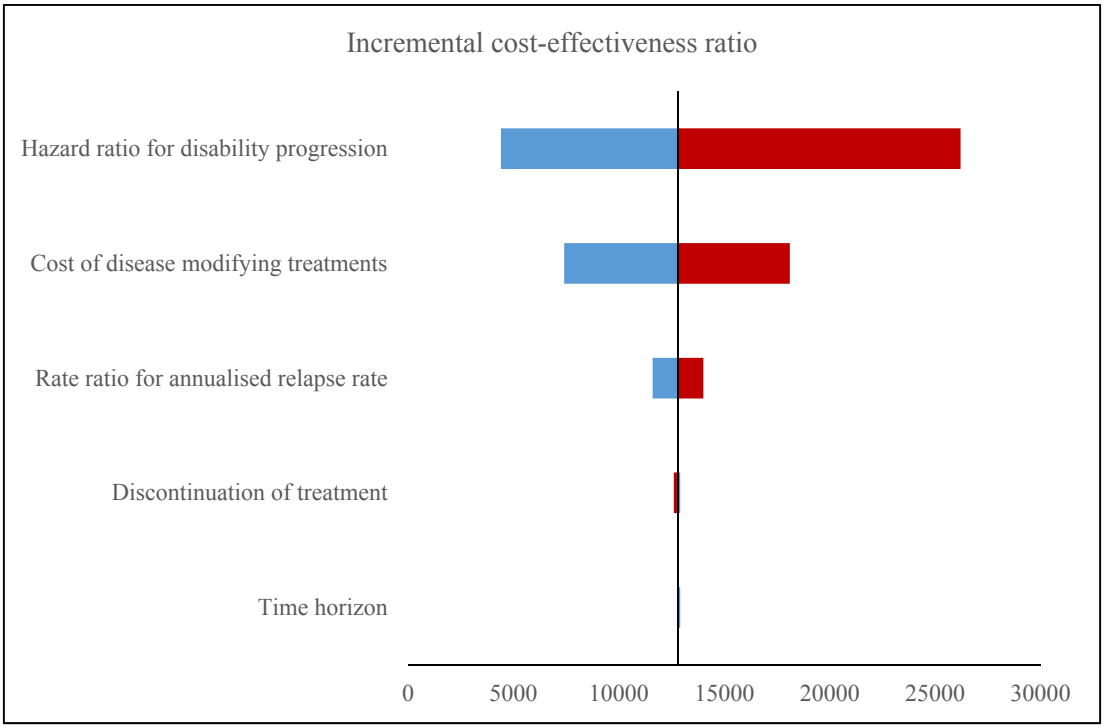


Figure 1: Base case tornado diagram for DMTs vs. best supportive care



In Figure 2, we show the impact **on the model estimated in SA 1** of varying model input parameters on the cost-effectiveness results. In SA 1, model input parameters were based on pooled estimates of treatment effectiveness for on-scheme DMTs. To determine the robustness of these results we varied the hazard ratio for disability progression, the rate ratio for annualised relapse rates, cost of disease modifying treatments, the annual discontinuation rate, and the model time horizon. The results show

that the model was sensitive to changes to the cost of disease modifying treatment. An increase by 10% in cost of disease modifying treatment led to an increase in the incremental cost-effectiveness ratio by 41%. A decrease by 10% of the cost of DMTs led to a decrease in the ICER by approximately 42%. These results remained robust to changes made to annualised relapse rate, model time horizon and discontinuation of treatment.

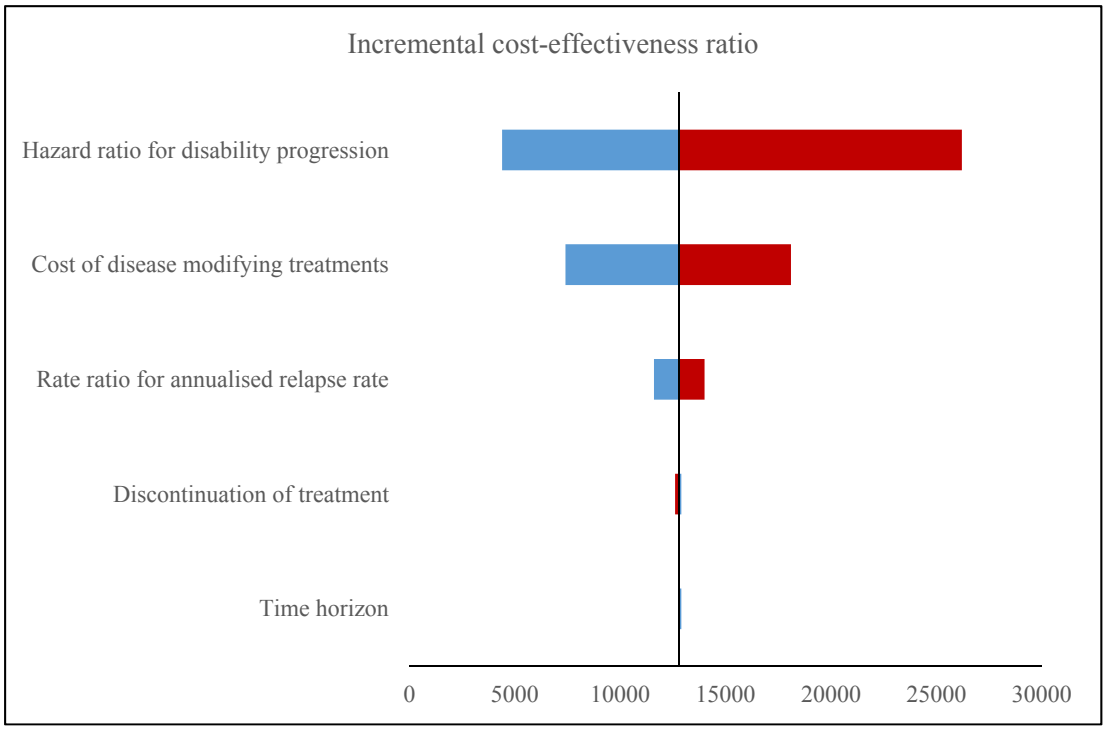


Figure 2: SA 1 tornado diagram for DMTs vs. best supportive care

Probabilistic sensitivity analysis conducted on the base case

Table 8 presents the results of the probabilistic sensitivity analysis **conducted on the base case,** that is, when the RSS data were used to estimate the hazard ratio for disability progression and the rate ratio for annualised relapse rates. These results show that the disease modifying treatment strategy was more costly and more effective than best supportive care, with an ICER of approximately £34,000 per QALY gained.

Table 8: Findings from the probabilistic sensitivity analysis conducted on the base case

Strategy	Mean cost(£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	363,600	-	8.64	-	-
Disease modifying treatments	395,200	31,600	9.57	0.93	34,000
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Figure 3 shows the cost-effectiveness plane for the results from the 1000 simulations from the probabilistic sensitivity analysis conducted on the base case, and Figure 4 shows the proportion of these simulations at various willingness-to-pay thresholds in the form of a cost-effectiveness acceptability curve. The cost-effectiveness plane shows that all of the simulations are in the north-east quadrant, where disease modifying treatments are more effective and more costly than best supportive care. We believe that the hazard ratio for disability progression is likely to be one of the key drivers of the economic model. The results from the cost-effectiveness acceptability curve show that at a willingness-to-pay threshold of £30,000 per QALY, disease-modifying treatment when compared to best supportive care, has a probability of being cost-effective of 0.23.

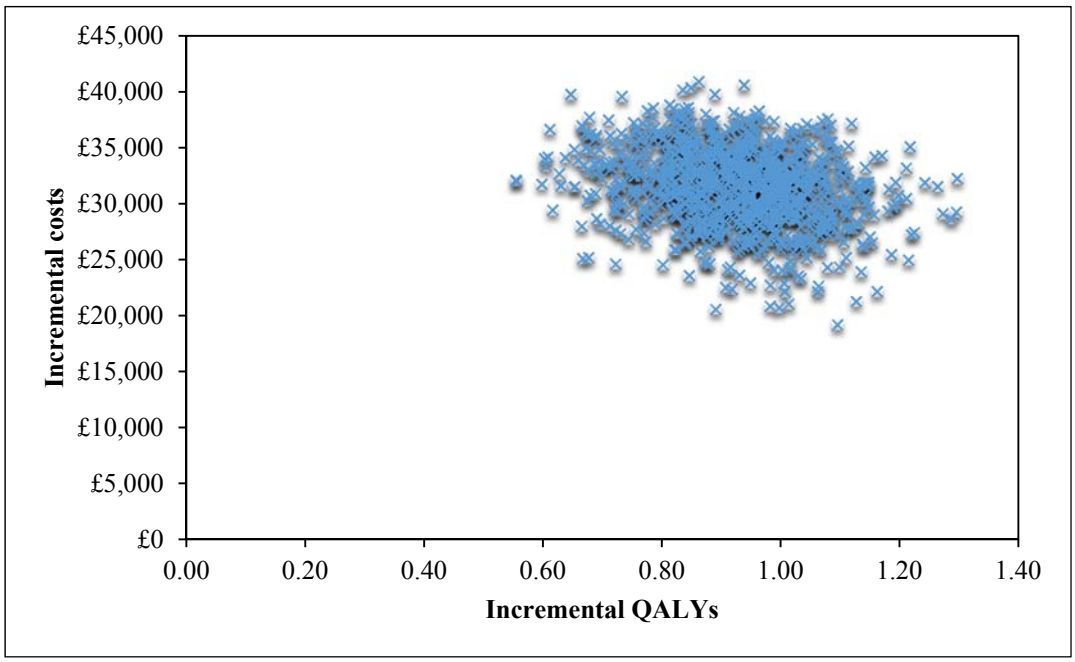


Figure 3: Cost-effectiveness plane, probabilistic sensitivity analysis conducted on the base case

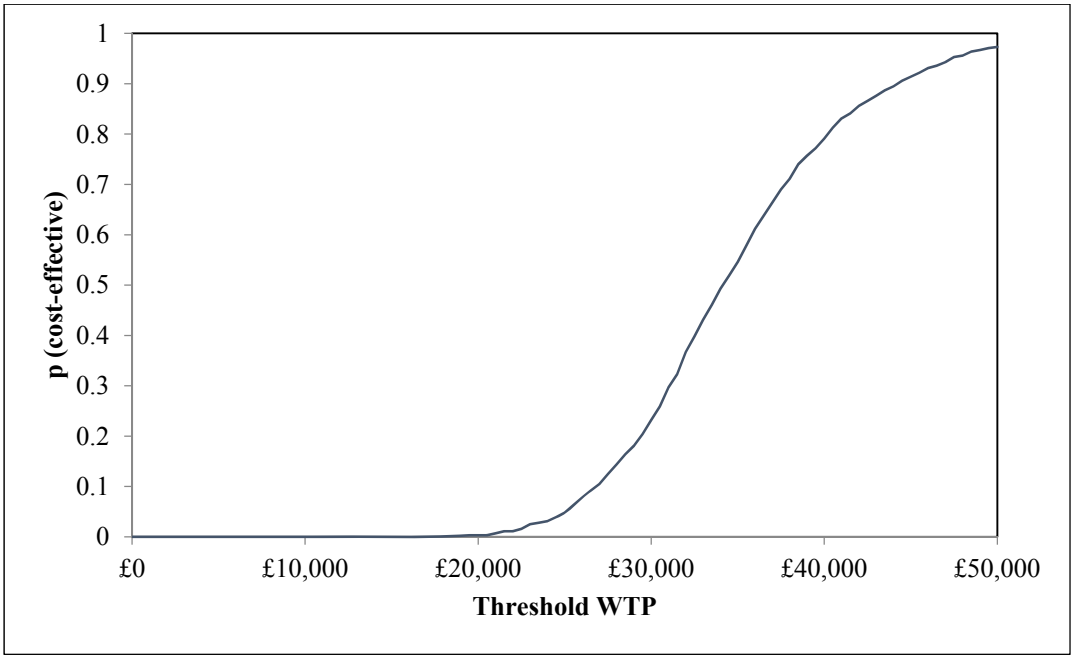


Figure 4: Cost-effectiveness acceptability curve, probabilistic senstivity analysis conducted on the base case

Probabilistic sensitivity analysis conducted on SA 1

Table 9 presents the results of the probabilistic sensitivity analysis when the findings from the assessment group review were used to estimate the pooled hazard ratio for disability progression and the pooled rate ratio for annualised relapse rates. The probabilistic sensitivity analysis shows that the ICER for disease modifying treatments compared to best supportive care was approximately £10,100 per QALY gained.

Table 9: Findings from the probabilistic sensitivity analysis conducted on SA 1

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	363,500	-	8.635	-	-
Disease modifying treatments	383,100	19,600	10.573	1.938	10,100
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Results from the simulations are also presented on a cost-effectiveness plane (Figure 5), and cost-effectiveness acceptability curve (Figure 6). Results from 1000 simulations show that a substantial number of points are in the northeast quadrant. Importantly, a significant number of simulations from the PSA were in the southeast quadrant, where disease-modifying treatments could be considered more effective and less costly than best supportive care. The results from the cost-effectiveness acceptability curve show that at a willingness-to-pay threshold of £30,000 per QALY, and when compared to best supportive care, disease-modifying treatment has a probability of being cost-effective of 0.84.

Through visual inspection of the cost-effectiveness plane, it appears that the incremental costs of providing disease modifying treatments is correlated with the incremental effects from receiving treatment. We have undertaken further model simulations (not presented here). We kept the hazard ratio for disability progression constant, and varied other parameters. This resulted in the majority of the plots concentrated in the northeast quadrant and there was no correlation seen. This finding, in addition to the PSA findings presented in Figure 5 and Figure 6, highlight the fact that the hazard ratio for disability progression is likely to be one of the key drivers in the economic model. The more effective DMTs are in slowing disease progression, the more likely they are to be cost-effective.

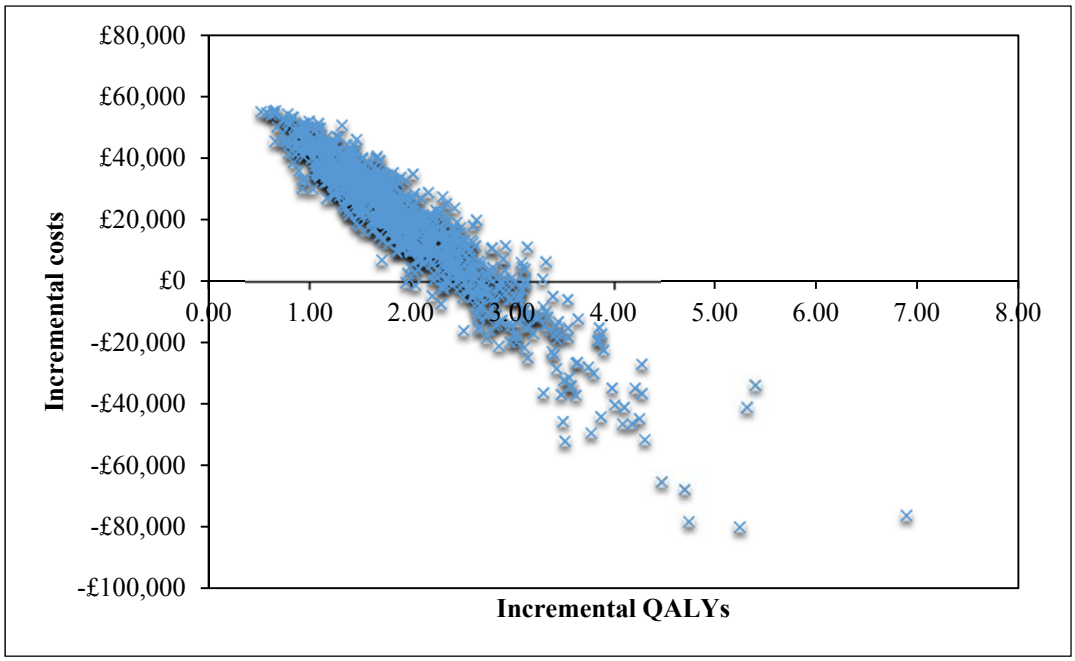


Figure 5: Cost-effectiveness plane, probabilistic sensitivity analysis conducted on SA 1

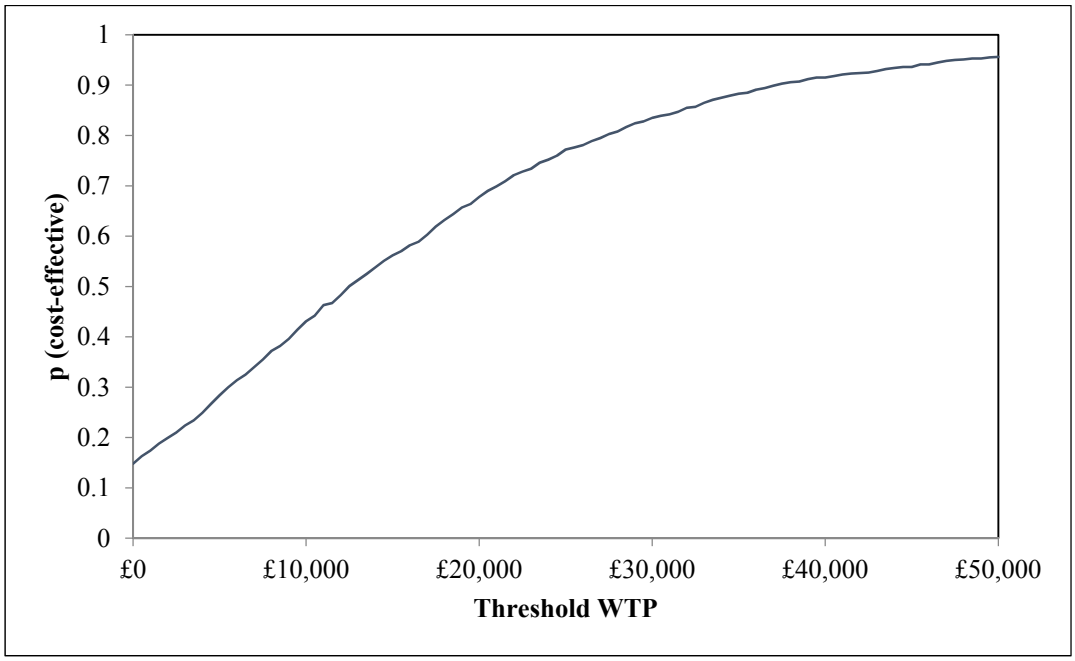


Figure 6: Cost-effectiveness acceptability curve, probabilistic sensitivity analysis conducted on SA 1

Results based on the CIS model

1.1 *Results of cost-effectiveness analysis*

1.1.1 Base case cost-effectiveness analysis

In Table 10, results for the base case analysis shows that providing best supportive care for people with CIS and continuing best supportive care on conversion to RRMS was the least costly strategy, with a mean cost of approximately £136,800, and the least effective, with a mean 12.78 QALYs gained. The strategy whereby people with CIS receive treatment with glatiramer acetate 20 mg SC daily (Copaxone), then receiving DMT when they convert to RRMS, dominated the IFN β-1a 30 µg IM once weekly (Avonex) and IFN β-1a 44 µg SC three times weekly (Rebif) treatment strategies. Excluding all dominated and extendedly dominated strategies, the optimal strategy was treatment with glatiramer acetate 20 mg SC daily (Copaxone). In comparison to best supportive care, providing glatiramer acetate 20 mg SC once daily (Copaxone) for patients with CIS, and DMTs on progression to RRMS, was associated with an ICER of £16,500 per QALY gained.

Table 10: Base case results, cost per QALY

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	136,800	-	12.78	-	-
BSC for CIS and DMTs for RRMS	176,400	39,600	13.16	0.38	Extendedly dominated
IFN β-1b 250 µg SC every other day (Betaferon/Extavia) for CIS and DMTs for RRMS	216,800	80,000	16.85	3.69	Extendedly dominated
Glatiramer acetate 20 mg SC daily (Copaxone) for CIS and DMTs for RRMS	235,200	98,400	18.73	5.95	16,500
IFN β-1a 30 µg IM once a week (Avonex) for CIS and DMTs for RRMS	252,100	16,900	18.57	-0.16	Dominated
IFN β-1a 44 µg SC three times per week (Rebif) for CIS and DMTs for RRMS	260,300	25,100	17.61	-1.12	Dominated

1.1.2 SA 1: Changing the time horizon to 20 years and 30 years

Table 11 and Table 12 show the findings when the model was run over time horizons of 20 years and 30 years. Over these shorter time horizons, treatment of CIS with glatiramer acetate 20 mg SC daily (Copaxone) remains cost-effective. Over these shorter time horizons, treatment with IFN β-1a 30 µg IM weekly (Avonex) or IFN β-1a 44 µg SC (Rebif) continues to be dominated by glatiramer acetate 20 mg SC daily (Copaxone).

Table 11: SA 1 results (20-year time horizon)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	155,100	-	10.33	-	-
BSC for CIS and DMTs for RRMS	166,400	21,600	10.73	0.40	Extendedly dominated
IFN β-1b 250 µg SC every other day (Betaferon/Extavia) for CIS and DMTs for RRMS	181,600	33,600	11.99	1.66	Extendedly dominated
Glatiramer acetate 20 mg SC daily (Copaxone) for CIS and DMTs for RRMS	190,400	42,700	12.46	2.13	20,000
IFN β-1a 30µg IM weekly (Avonex) for CIS and DMTs for RRMS	204,100	13,400	12.39	-0.07	Dominated
IFN β-1a 44 µg SC three times weekly (Rebif) for CIS and DMTs for RRMS	215,000	24,000	12.15	-0.31	Dominated

Table 12: SA 1 results (30-year time horizon)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	173,100	-	12.02	-	-
BSC for CIS and DMTs for RRMS	197,100	24,000	12.46	0.44	Extendedly dominated
IFN β-1b 250 µg SC every other day (Betaferon/Extavia) for CIS and DMTs for RRMS	220,600	47,500	14.89	2.87	Extendedly dominated
Glatiramer acetate 20 mg SC daily (Copaxone) for CIS and DMTs for RRMS	234,700	61,600	15.88	3.86	16,000
IFN β-1a 30µg IM weekly (Avonex) for CIS and DMTs for RRMS	249,800	15,100	15.78	-0.10	Dominated
IFN β-1a 44 µg SC three times weekly (Rebif) for CIS and DMTs for RRMS	259,300	24,600	15.28	-0.60	Dominated

1.1.3 SA 2 Assuming 5% of people with CIS would discontinue treatment with DMTs

Table 13 shows the findings when we assumed that approximately 5% of those treated with DMTs for CIS discontinue treatment every year. In this scenario, the treatment of CIS with IFN β-1b 250 µg SC every other day was cost-effective, with an ICER of £15,100/QALY gained. Treatment with glatiramer acetate 20 mg SC daily (Copaxone) remains cost-effective. However, treatment with IFN β-1a 30µg IM weekly (Avonex) or IFN β-1a 44 µg SC three times weekly (Rebif) continues to be dominated or associated with an extremely high ICER.

Table 13: SA 2 results (yearly discontinuation rate of 5%)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
BSC (CIS and RRMS)	136,800	-	12.78	-	
BSC for CIS and DMTs for RRMS	176,400	39,600	13.16	0.38	Extendedly dominated
Glatiramer acetate 20 mg SC daily (Copaxone) for CIS and DMTs for RRMS	209,800	73,000	16.22	3.44	Extendedly dominated
IFN β-1b 250 µg SC every other day (Betaferon/Extavia) for CIS and DMTs for RRMS	211,500	74,700	16.36	3.58	20,900
IFN β-1a 30µg IM weekly (Avonex) for CIS and DMTs for RRMS	224,700	13,200	16.31	-0.05	Dominated
IFN β-1a 44 µg SC three times weekly (Rebif) for CIS and DMTs for RRMS	242,300	30,800	16.41	0.05	616,000

In Figure 7, we present graphically the impact of varying model input parameters on the cost-effectiveness results. To determine the robustness of the results, we varied the utlity value for the CIS health state and the probability of treatment discontinuation as well as the mode of drug administration, the disutility associated with adverse events and the annual cost of BSC. The results show that the model was most sensitive to a +/- 10% change in the utility of the CIS health state. A 10% increase in the health state utility of CIS would take the value to 0.6898. However, this would still give an ICER for glatiramer acetate 20 mg (Copaxone) vs. BSC of £18,600, well within the normal expected levels of willingness to pay.

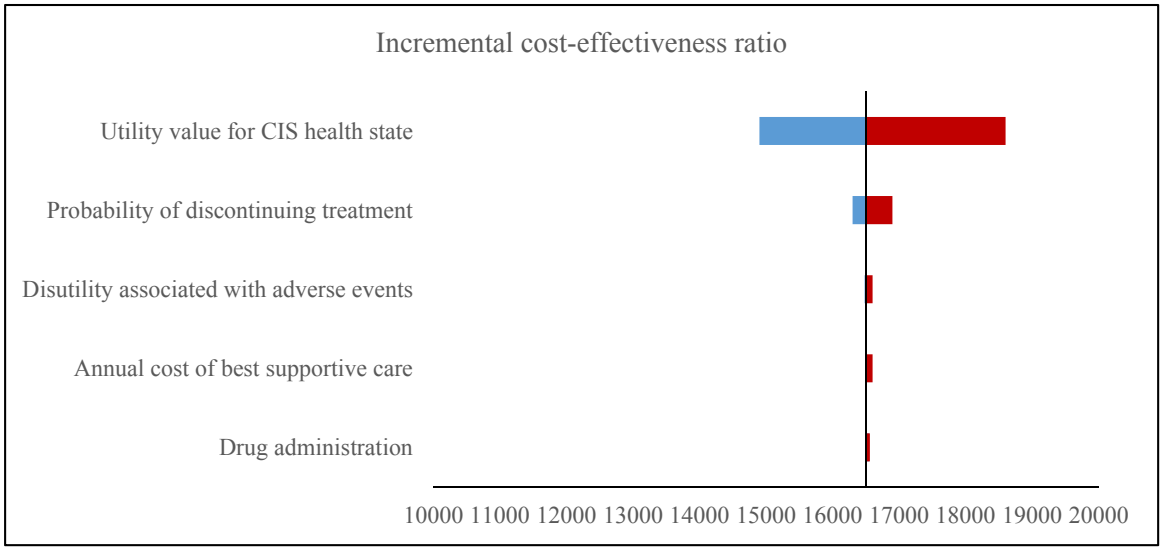


Figure 7: Tornado diagram for glatiramer acetate 20 mg SC daily vs. BSC

2 Appendix 9: Additional analyses undertaken by the assessment group

2.1 *Time-varying model*

In Table 14 the results are presented in terms of cost per QALY for the time varying model. Analyses use information from the NMA in the time-varying treatment effect model. These results showed that the disease modifying strategy was more costly and more effective than best supportive care alone. Disease modifying strategy was approximately £33,600 more costly than best supportive care and produced 1.461 more QALYs, which equated to an ICER of approximately £23,000 per QALY. This indicates that for every additional QALY from disease modifying treatments there is an incremental cost of £23,000.

Table 14: Results based on cost per QALY, time-varying model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
Disease modifying treatments	395,700	33,600	10.125	1.461	23,000
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years;					

SA 2a: Individual drugs from assessment group review, progression confirmed at 3 months and individual drug annualised relapse rate

Results based on the time varying model by individual drug showed that best supportive care was the least costly and least effective strategy (see Table 15). Glatiramer acetate treatment strategy was approximately £26,300 more expensive than the best supportive care treatment strategy and produced 1.105 more QALYs with an ICER of approximately £2700 per QALY. IFN β-1b 250µg every other day (Betaferon/Extavia) and IFN β-1a 125µg (Plegridy) were both shown to be cost-effective with ICERs of approximately £5700 and £9900 per QALY, respectively. Both IFN β-1a 30 µg IM (Avonex) and IFN β-1a 44 µg SC (Rebif) were dominated by IFN β-1a 125 µg (Plegridy).

Table 15: Results based on the time-varying model, SA 2a

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
Glatiramer acetate 20mg (Copaxone)	388,400	26,300	9.770	1.105	2,700
IFN β-1b 250 µg every other day (Betaferon/Extavia)	390,500	2100	10.139	0.369	5700

IFNβ-1a 125µg (Plegridy)	395,500	5,000	10.642	0.503	9,900
IFNβ-1a 30µg IM (Avonex)	415,900	20,400	9.994	-0.648	Dominated
SC INFβ-1a 44µg (Rebif)	416,100	20600	10.420	-0.222	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous					

SA 2b: Individual drugs from AG review, progression confirmed at 6 months, and individual drug annualised relapse rate

In Table 16, we report the results based on the time varying model. These results show that IFNβ-1a 125µg (Plegridy) dominated all other disease modifying treatment strategies. When compared to best supportive care, IFN β-1a 125 µg (Plegridy) was more expensive and effective and had an ICER of approximately £3200 per QALY.

Table 16: Results based on the time-varying model, SA 2b

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	8.664	-	-
IFNβ-1a 125µg (Plegridy)	371,500	9400	11.608	2.944	3200
SC INFβ-1a 44µg (Rebif)	395,700	24,200	11.290	-0.318	Dominated
Glatiramer acetate 20mg (Copaxone)	396,500	25000	9.485	-2.123	Dominated
IM IFNβ-1a 30µg (Avonex)	409,200	37700	10.267	-1.341	Dominated
BSC, best supportive care; IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

2.2 *Incorporating carers' disutilities*

We present analyses below relating to the base run model.

2.2.1 Cost-effectiveness analysis results: base case and sensitivity analyses

Base Case

In Table 17, we present the findings from our base case analysis with the inclusion of carers' disutilities. The results showed that the disease modifying treatment strategy was more costly and more effective than best supportive care. The expected mean costs per person for the disease

modifying treatment strategy were approximately £31,900 more costly than the best supportive care strategy and produced 1.046 more QALYs with an ICER of approximately £30,500 per QALY.

Table 17: Base case results based cost per QALY

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
Disease modifying treatments	394,000	31,900	8.194	1.046	30,500
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

SA 1: Pooled on-scheme DMTs from assessment group review

We used two key estimates of treatment effectiveness from our clinical effectiveness review: the aggregated hazard ratio for disability progression confirmed at 3 months and the aggregated annualised relapse rate.

In Table 18, the results show that disease modifying treatment strategy was more costly and more effective than best supportive care alone. The disease modifying treatment strategy was approximately £23,300 more costly than best supportive care and produced 2.031 more QALYs, which equated to an ICER of approximately £11,500 per QALY.

Table 18: Cost per QALY, SA 1

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
Disease modifying treatments	385,400	23,300	9.179	2.031	11,500
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

SA 2a Individual drugs from AG review, progression confirmed at 3 months (preferred analysis)

Table 19: Cost per QALY, SA 2a (assessment group estimates of relapse rate and disability progression confirmed at 3 months)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
IFN β-1a 125µg (Plegridy)	379,900	17,800	10.016	2.868	6200
Glatiramer acetate 20mg (Copaxone)	381,000	1100	8.646	-1.552	Dominated
IFN β-1b 250 µg every other day (Betaferon/Extavia)	393,400	13,500	8.556	-1.46	Dominated
INF β-1a 44µg SC (Rebif)	404,800	24,900	9.614	-0.402	Dominated
IFNβ-1a 30µg IM (Avonex)	406,100	26,200	9.027	-0.989	Dominated
IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous					

The results in Table 19, were robust to the inclusion of carers' disutilities. These results showed that IFN β-1a 125 µg (Plegridy) remained dominant over all other disease modifying treatment strategies. When compared to best supportive care, IFN β-1a 125 µg (Plegridy) was approximately £17,800 more costly and was more effective by expected mean gains of QALYs, with an ICER of £6200 per QALY.

SA 2b: Individual drugs from AG review, progression confirmed at 6 months

Likewise, these results were robust when we included carers' disutilities in the analysis. Results showed that IFN β-1a 125 µg SC every two weeks (Plegridy) remained dominant over all other strategies included in this analysis (see Table 20).

Table 20: Cost per QALY, SA 2b (assessment group estimates, disability progression confirmed at 6 months)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
IFN β-1a 125 µg SC every two weeks (Plegridy)	347,000	-	11.584	-	-
Best supportive care	362,100	15,100	7.148	-4.436	Dominated
IFN β-1a 44 µg SC three times a week (Rebif)	377,600	30,600	10.966	-0.618	Dominated
Glatiramer acetate 20 mg SC daily (Copaxone)	391,900	44,900	8.236	-3.348	Dominated

IFN β-1a 30 µg IM once weekly (Avonex)	396,900	49,900	9.446	-2.138	Dominated

BSC, best supportive care; IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous

SA 3: Hazard ratios from company submissions

When we used the estimates for treatment effectiveness (annualised relapse rate and disability progression) reported by each company and included carers' disutilities, these results showed [redacted] 21[redacted] When compared to best supportive care, IFN β-1a 125 µg (Plegridy) resulted in an ICER of [redacted] per QALY.

Table 21: Cost per QALY, SA 3 (company estimates of effectiveness)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
IFN β-1a 125 µg SC every two weeks (Plegridy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 40 mg SC three times weekly (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 30µg IM once weekly (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44µg SC three times a week (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; RSS, risk sharing scheme; SC, subcutaneous

SA 4: Time horizon changed from 50 years to 20 and 30 years

Table 22 and Table 23 show the results based on a 20-year and 30-year time horizon, respectively. Findings showed that the glatiramer acetate treatment strategy continued to be extendedly dominated by IFN β-1a 125 µg (Plegridy) in both analyses, with the inclusion of carers' disutilities. Additionally, IFN β-1a 125 µg (Plegridy) dominated both IFN β-1a 30 µg IM (Avonex) and IFN β-1a 44µg SC (Rebif) treatment strategies. Excluding all dominated strategies, IFN β-1a 125 µg (Plegridy) when compared to best supportive care had an ICER of approximately £ and £ per QALY for the 20-year and 30-year time horizon, respectively.

Table 22: Cost per QALY, SA 4 (time horizon changed to 20 years)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	196,900	-	5.710	-	-
Glatiramer acetate 20mg (Copaxone)	220,500	23,600	6.628	0.918	Extendedly dominated
IFNβ-1a 125µg (Plegridy)	225,800	28,900	7.301	1.591	18,200
IFNβ-1a 30µg IM (Avonex)	242,600	16,800	6.789	-0.512	Dominated
IFN β-1a 44µg SC (Rebif)	245,200	19,400	7.156	-0.145	Dominated

IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous

Table 23: Cost per QALY, SA 4 (time horizon changed to 30 years)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	279,400	-	6.540	-	-
Glatiramer acetate 20mg (Copaxone)	298,900	19,500	7.790	1.25	Extendedly dominated
IFNβ-1a 125µg (Plegridy)	300,400	21,000	8.809	2.269	9300
INFβ-1a 44µg SC (Rebif)	322,900	22,500	8.551	-0.258	Dominated
IFNβ-1a 30µg IM (Avonex)	323,000	22,600	8.057	-0.752	Dominated

IFN, interferon; ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous

BAYER COMMENTS ON THE ASSESSMENT GROUP'S ADDENDUM REPORT

The final scope for this MTA says that NICE will appraise beta interferon and glatiramer acetate at their current NHS prices, and using additional data on long-term outcomes from the risk sharing scheme (RSS), to determine whether these technologies are now cost effective. To do so, NICE has determined that it needs to appraise these technologies within the context of the original appraisal (Technology Appraisal 32). That is, beta interferon and glatiramer acetate should be compared with best supportive care (BSC). On this basis, we believe that the assessment of each product based on pairwise comparisons relying on RSS data would be in contrast with the remit of the current NICE MTA. Moreover, the RSS was not set up as a comparative study and was not blinded. Choice of disease modifying therapy (DMT) was physician determined dependent on patient characteristics; eg beta-interferon 1b patients had a worse Expanded Disability Status Scale (EDSS) compared to the other products under appraisal. As such, the outcomes from individual DMTs are not directly comparative and implementation of pairwise cost-effectiveness analyses will generate biased results.

In conclusion, we believe the base case analysis should avoid any sort of pairwise comparison among the technologies under appraisal and consider them as part of a class of drugs with exchangeable effects, as stated by clinical experts during the first Appraisal Committee meeting. The approach proposed by the Assessment Group (AG) to use a pooled class effect and individual costs for the technologies considered in this MTA is therefore the one that best reflects the clinical experience accrued by clinicians whilst administering these products since their availability to patients in the UK.

Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]
Addendum consultation – Biogen Idec response

Our principal goals and recommendations for progress

1. Biogen believe at the conclusion of this multiple technology appraisal (MTA) process, positive guidance should remain in place for all the disease modifying therapies (DMTs) included as they provide a viable, effective and relatively safe alternative for the management of relapsing remitting multiple sclerosis (RRMS).
    - Multiple Sclerosis (MS) is a heterogeneous disease with important variation in clinical and patient-related measures. Clinicians and patients should continue to have access to the full and varied range of effective DMTs that help address the specific lifestyle needs and preferences of patients.
    - Although these treatments are used within the same patient population, each has a different value proposition attributed to differential efficacy and safety profiles coupled with unique administration routes (subcutaneous or intramuscular),dosing frequencies (every day to every 2 weeks) and monitoring requirements.

2. With respect to the UK Risk Sharing Scheme (RSS), Biogen was a proactive and supportive participant of this initiative that delivered widely acknowledged benefits to both patients and to the NHS. However it is important to use the data accumulated from this scheme appropriately, in accordance with the integrity of the study design and objectives.
    - Due to, in part, the continued contribution of Biogen and other RSS fund holders into the NHS infrastructure, there are now (1):
        - Over 72 centres that now have specialist teams providing MS expertise to all patients across the UK
        - Over 235 MS specialist nurses are now working across the UK providing clinical advice to MS patients.
    - The RSS was never designed as a cross-comparative study and should not be used as such. It should be used solely as a mechanism to ensure that each product provides value to the NHS, as expressed in terms of the measures specifically designed for the purposes of the RSS.
    - According to these measures in the final year 10 analysis, all of the included DMTs were considered to be both clinically and cost-effective vs best supportive care (BSC) at current agreed prices and dependent upon agreements that have positively contributed to the service provision and optimisation cited above. Once a consensus is reached on the proposed primary evidence base and methodology for assessing the DMTs included in this process, Biogen is willing to discuss initiatives to ensure the ongoing availability of IFN β-1a 30µg (Avonex) to new and existing patients including our ongoing contributions to infrastructure investment.

3. Given the desire of Biogen and the MS community to retain access to these DMTs that have demonstrated their effectiveness and value to the NHS in the past 15 years, we suggest that an incremental analysis of DMTs against each other is an inappropriate exercise. We believe that the purpose of the MTA is not to select a “winner”, but rather to ensure that all products included are cost-effective vs BSC (i.e. no treatment) representing the first line use of these DMTs in patients with active RRMS and clinically isolated syndrome (CIS) where relevant.
    - Any deviation from this approach and conclusion would risk the destabilisation of approximately 13,000 MS patients currently receiving these effective DMTs (many of whom have been on treatment for a number of years), ultimately leading to a negative impact on patient outcomes and increased costs borne by the NHS.

- We therefore suggest that the analyses reported in Tables 15-19 and 29-33 of the addendum should be omitted from the discussion for clarity of decision making. These “incremental analyses of on-scheme DMTs using RSS data” are tangential to the scope of this MTA and should be removed.

4. We find the representation of SC pegylated IFN β-1a 125 µg (Plegridy) in the addendum to be unsatisfactory given conclusions and outcomes reported in the first AG report. We are firmly against the inclusion of in any SC pegylated IFN β-1a 125 µg analysis where the RSS is used as the primary evidence base for clinical outcomes in cost-effectiveness assessment, as it was never part of the RSS study, that pivotal clinical studies indicate superior relapse rate reduction and disability progression data and therefore you cannot attribute the outcomes of the RSS study to SC pegylated IFN β-1a 125 µg. Biogen suggest that individual treatment effects from network meta-analyses (NMA) should be the preferred evidence base for estimation of cost effectiveness. Biogen is of the opinion that SC pegylated IFN β-1a 125 µg is penalised in the suggested MTA approach because it was not included in the scheme and there exists a robust body of clinical evidence existing on a number of important clinical endpoints that could be used to generate a comprehensive assessment of this DMT within the scope of this MTA.

5. We consider there to be a number of inconsistencies in the presentation of analyses and assumptions in the AG’s latest analyses:
    - The incremental analyses discussed above use individual efficacy estimates from the RSS, but when SC pegylated IFN β-1a 125 µg is subsequently considered, only a pooled class effect is applied, and no incremental analyses are provided.
    - We are also unsure about the treatment of glatiramer acetate (GA) 20mg in these analyses – on what basis is it treated separately to the β-interferons?
    - Furthermore GA 40 mg was excluded from the evaluated DMTs. Currently, there is no guidance regarding this dose or any explanation of how this will be evaluated.
    - Biogen are uncertain why the AG have deviated from original analyses using RSS entry prices and have now conducted analyses using list prices that lead to notably higher ICERs. It should be noted that the 2002 Health Service Circular(2) publically references the agreed entry prices of RSS DMTs. It is also uncertain whether current commercial medicines unit (CMU) prices are appropriate for cost-effectiveness assessment if NICE are no longer considering other RSS commercial arrangements in its assessment.

Acknowledging the limitations of the RSS design, outcomes, and findings

6. The RSS does not lend itself easily to a robust analysis of the cost-effectiveness of DMTs, and should not be used inappropriately to fill data gaps in this challenging assessment. We note that the NICE reference case(3) states:
    - "…the scope identifies principal measures of health outcome(s) that will be relevant for the estimation of clinical effectiveness. That is, they measure health benefits and adverse effects that are important to patients and/or their carers." (Para 2.2.8).
    - "…the evidence submitted to the Appraisal Committee should be… assembled systematically and synthesised in a transparent way that allows the analysis to be reproduced; ….analysed in a way that is methodologically sound and, in particular, minimises any bias." (Para 3.2.1)
    - "…RCTs are… considered to be most appropriate for measures of relative treatment effect." (Para 3.3.2)

7. The measures captured in the RSS do not lend themselves to a clear, comparative assessment of cost effectiveness as intended within the MTA:
    - In the RSS, the main outcome measure was the change relative to baseline of a weighted sum of the proportions of patients who have progressed to each expanded disability status scale (EDSS) score; the weighting factors were loss of utility of patients in each EDSS, relative to the utility of 1 for perfect health. We question whether this outcome is the most pragmatic or meaningful in our efforts to clarify and quantify the value of DMTs to the NHS community.
    - The implied hazard ratios and the deviation scores are calculated to describe the relationship between the RSS outcomes and the disease progression captured in the British Columbia dataset, not the comparative effects of these treatments compared with BSC in a specific population of MS patients.
    - There appears to be no independent evidence to support the existence of a waning effect, other than in the documentation of the RSS. We are unaware of any long term efficacy data published from any of the international MS registries for example, that might corroborate this effect. We are sceptical that a biological process could be characterized accurately by an immediate reduction in efficacy of 50% after 10 years of 100% efficacy. Its inclusion in the model further limits the applicability of the RSS to meaningful decision making in the current era.

8. As noted in BMJ editorial on the 6-year outcomes of the RSS: *"There are limitations inherent to the nature of the project. This is not a randomised controlled trial and unrecognised biases may be driving the observed effect. Geographical, ethnic or temporal differences probably do not explain the divergence in the cohorts, but there may be unappreciated differences in patient selection or retention. It should be remembered, however, that this was not established as the definitive scientific trial on the long-term efficacy of disease-modifying therapies: it is a health policy initiative to determine, within acceptable margins, whether the NHS pays too much for multiple sclerosis drugs"*.(4)

9. In conclusion, there are major limitations in the design and outcomes of the RSS that caution against over-interpretation or inappropriate use of this data source.

SC pegylated IFN β-1a 125 µg – demonstrated efficacy through RCT and long-term extension study data

10. There is a large body of evidence to support the high clinical efficacy of SC pegylated IFN β-1a 125 µg in patients with RRMS. Moreover, the design of the pivotal clinical study (2 years duration, primary outcome measured at 1 year) was endorsed by the European Medicines Agency (EMA) and is a robust foundation for the demonstration of clinical efficacy. We reject any suggestion to the contrary. Furthermore, extension studies have shown that the benefits of SC pegylated IFN β-1a 125 µg every 2 weeks (Q2W) are maintained to at least 4 years.

    The CHMP's assessment report for Plegridy (5) stated that:

    - "…in light of the extensive experience gained with this class, …the requirements laid down in the current MS guideline …would apply only partially, for example in terms of study duration and the duration of placebo control."
    - Moreover, "…both studies covered a period of 2 years, which is in line with the current recommendation for MS studies. However, the efficacy claim was primarily supported by the one-year placebo-controlled data derived from study 301. Two year efficacy data were provided during the course of the assessment, which was considered sufficient by the CHMP to provide supportive data for the demonstration of maintenance of the effect. …data for 2 years treatment supported maintenance of the effect beyond year 1."

11. The pivotal phase 3 study ADVANCE was a 2-year, randomised, double blind study with duration of 2 years. The primary efficacy endpoint was annualised relapse rate (ARR) at 1 year. At the conclusion of the 2-year study, patients were eligible to enter a 2-year extension study (ATTAIN). As per the Summary of Product Characteristics (SmPC) (updated December 2016), 658 patients have completed 4 years in this study programme (6). A total of 2,000 patient-years of experience were accumulated in ADVANCE.

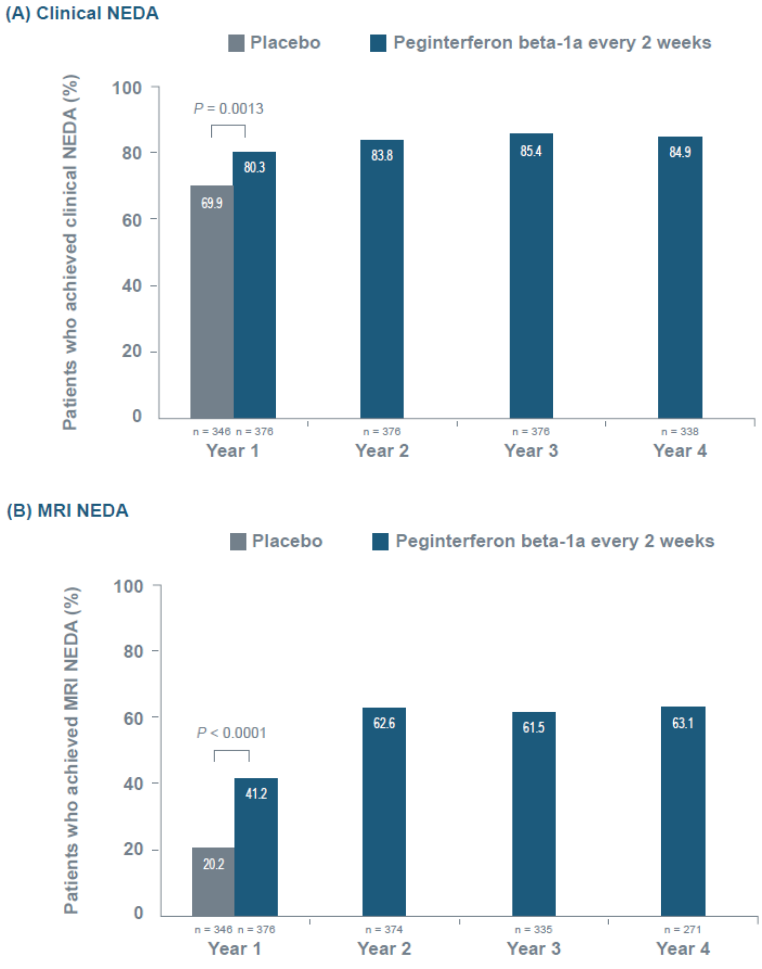
    On all measures of confirmed disability progression, Plegridy demonstrated statistically significant differences versus placebo: (Table 10, EMA assessment report (5)):

    - Confirmed disability progression at 3 months (CDP3M) over 1 year (pre-specified outcome measure)
    - CDP at 6 months (CDP6M) over 1 year
    - CDP6M over 2 years (complete 2 year results)

12. Although not incorporated into the NMA, the maintenance of SC pegylated IFN β-1a 125 µg Q2W effect has been clinically and radiologically proven. In ATTAIN, the extension trial of ADVANCE, SC pegylated IFN β-1a 125 µg Q2W demonstrated a consistent, sustained effect on both clinical and radiological outcomes with long-term treatment.
    - Some efficacy and safety analysis of ATTAIN were presented in Biogen's submission for the MTA [ID809] (section 3.3.2.4, pages 86 & 87). Information provided was from two posters presented at the 68th American Academy of Neurology (AAN) in 2016.
    - In Fiore et al. (7), patients receiving continuous SC pegylated IFN β-1a Q2W (since Year 1 of the ADVANCE trial; n=376 ATTAIN intent-to-treat (ITT) population) continued to show low adjusted ARR into Year 6 and low mean number of MRI lesions (new T1, new/newly enlarging T2, Gd+) up to Year 4 .
    - In Cui et al. (8), the safety and tolerability of SC pegylated IFN β-1a 125 µg Q2W remained favourable up to 5 years and there were no marked changes in event rates for any AEs (safety profile was consistent with that observed during the ADVANCE trial).

- In addition to these two posters, from Biogen's data on file (9), patients on SC pegylated IFN β-1a 125 µg Q2W since Year 1 of the ADVANCE trial continued to be associated with low CDP6M with 14% of the ATTAIN ITT population (n=376) with sustained disability progression at Year 6.

13. Additional information on the long-term efficacy of SC pegylated IFN β-1a 125 µg Q2W from ATTAIN was presented at the 32nd European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) in 2016 (10). SC pegylated IFN β-1a 125 µg Q2W demonstrated maintained effects on the achievement of no evidence of disease activity (NEDA), as assessed on a year-by-year basis over 4 years in the ATTAIN ITT population (n=376). The effect was noticed across clinical-, MRI-, and overall-NEDA (10)
    - At Year 1, significantly higher proportions of patients treated with SC pegIFNβ-1a 125 µg Q2W achieved (overall, clinical and MRI) NEDA from baseline to Week 48 compared with patients who received placebo (Figure 1: A, B, C) (10).
    - Patients who have been administered SC pegylated IFN β-1a 125 µg Q2W since year 1 of the ADVANCE trial maintained rates of (clinical, MRI and overall) NEDA over 4 years (Figure 1: A,B, C) (10).



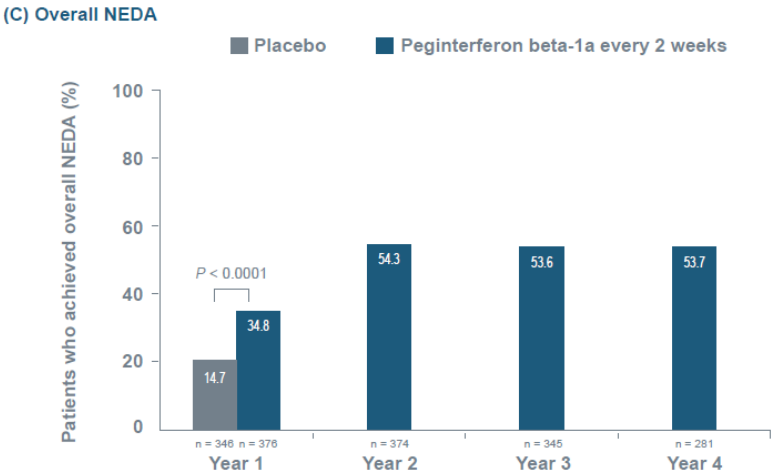


Figure 1 - Proportions of patients achieving NEDA by study year: ADVANCE and ATTAIN

14. In conclusion, we challenge the assertions that the clinical evidence for SC pegylated IFN β-1a 125 µg is not appropriate for inclusion in a comparative assessment, that its clinical study provides a weak evidence base for the NMA, or that the RSS is the best source for informative data on the longer term effectiveness of DMTs. We see no reason why SC pegylated IFN β-1a 125 µg should be excluded from key analyses, or that its proven clinical benefits from a robust clinical development programme should be overlooked in favour of a pooled class effect derived from the RSS.

Pooling the treatment effect of β-interferons is inappropriate

15. There are a number of reasons why pooling the effects of the β-interferons is not appropriate for this assessment:
    - There is a risk of loss of information inherent in any decision to invoke a class effect in the case of the β interferons. Pooling results into one hazard ratio masks the results of the individual agents and the variations in benefit/risk profiles associated with different posology, clinical efficacy, quality of life, safety and patient preferences that have been described throughout the post-authorisation history of these products.
    - The use of class effects has been rejected by NICE committees in the past, for example in TA388 (Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction). The ERG stated that "…the class effect for ACEs is an assumed effect by the Cochrane authors but is not proven and the ERG therefore considers the text to be factually correct". (11)
    - The threshold for acceptance of a class effect should necessarily be high, because "…typically, a decision on whether a drug acts similarly to other agents with a similar biological makeup is based on an evaluation of the empirical data and pharmacopathophysiologic reasoning. Because of the inadequacies of the former and the subjective nature of the latter, a rigorous and reproducible process is required to support the establishment of whether biologically similar drugs exert a class effect." (12)
    - From the conducted NMAs, only ARR results show similarity in point estimates. A pooled effect could be appropriate in such circumstances; however this does not extend to HRs for CDP and discontinuation rates, respectively influential of cost-effectiveness outcomes.
    - Given the repeated finding in sensitivity analyses that the HR for CDP is the major driver of cost-effectiveness results, it is unclear why the AG would choose to reject the depth of data that is available on this key efficacy measure in favour of selecting the pooled estimate from the RSS.

16. There are clear differences in reported HR estimates provided for CDP3M and CDP6M (Table 66 of the original report):
    - The pooled RSS effect on CDP was estimated at 0.7913 (excluding SC pegylated IFN β-1a 125 µg)
    - Pooled CDP3M estimation made by the AG NMA was 0.6955 (including SC pegylated IFN β-1a 125 µg)
    - Individual results derived from the NMA were between 0.6200 and 0.7800 for CDP3M and 0.3400 to 0.8200 for CDP6M. SC pegylated IFN β-1a 125 µg was rank first and second most effective in these analyses, respectively.

17. There are also differences in the results for discontinuations and adverse events (AEs) that are not currently captured in the cost-effectiveness assessment.
    - RSS discontinuation rate: 0.0500 assumption
    - Individual discontinuations reported by each manufacturer were from 0.0500 to 0.1040 and results of derived discontinuations from AG review were from 0.0150 to 0.0263
    - No results for AEs from the AG NMA have been reported. However, in the appendix H of Biogen's submission, when using Biogen's NMA, odds ratio (OR) for AEs and any serious adverse events (SAEs) versus placebo were presented (respectively in Figure 60 and Figure 62, original manufacturer submission). The safety data of included treatments were spread:
        - For any AEs, the results varied between 0.579 for GA 20 mg to up to 1.950 for IFN β-1a 30µg
        - For any SAEs, the results varied between 0.635 for IFN β -1a 30µg to 0.937 for IFN β-1b 44 µg

18. We challenge the assertion that the results of the NMA are "clinically unrealistic" in light of the robust methodology that was applied to generate the findings. We acknowledge gaps in the CDP6M network lead to fewer comparisons and sample sizes (hence the AG's preference for the CDP3M network which allows for all comparisons), but refer the AG to previous technology appraisals and literature that confirms the clinical view that CDP6M is a more robust measure of disease progression in MS. (13)

19. In the absence of a clear rationale to pool the efficacy data of the individual agents, we strongly advocate the use of individual estimates for both ARR and CDP using the highest quality available evidence from RCTs and NMAs.

Conclusion summary

Biogen would appreciate the consideration of the following points by NICE:

- There is a large body of evidence to support the high clinical efficacy of SC pegylated IFN β-1a 125 µg in patients with RRMS. Moreover, the design of the pivotal clinical study (2 years duration, primary outcome measured at 1 year) was endorsed by the EMA and is a robust foundation for the demonstration of clinical efficacy.
- The RSS was never designed as a cross-comparative study and should not be used as such. It should be used solely as a mechanism to ensure that each product provides value to the NHS, as expressed in terms of the measures specifically designed for the purposes of the RSS.
- It is contradictory that GA 40 mg was excluded from the evaluated DMTs and yet SC pegylated IFN β-1a 125 µg is subsequently considered using pooled class effect with no incremental analyses being considered
- Biogen believe at the conclusion of this MTA process, positive guidance should remain in place for all the IFN DMTs included as they provide a viable, effective and relatively safe alternative for the management of RRMS.

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Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]

Merck's response to Warwick Evidence additional report (addendum).

Executive Summary

Merck has been involved in the UK Risk Sharing Scheme (RSS) since its inception in 2002. The principles of the scheme have been outlined in the Department of Health Service Circular (HSC) and referred to again in this recent addendum by Warwick.

We welcome the position NICE has taken to acknowledge the majority of the scheme's assumptions and the use of the data from the scheme in their assessment of these products.

Merck views the principles of the RSS and the use of its data as intertwined and proposes that they should be utilised in the manner that the scheme was designed for, namely to assess individual product against Best Standard Care (BSC) equivalent. Pooling of RSS product data or use of the RSS to cross-compare products is an inappropriate use of the data, as articulated indirectly in the following extract from the HSC.

"The scheme relates solely to the cost effectiveness of the use of these products in the NHS; it is not intended and should not be represented as a further "clinical" trial of the clinical efficacy of the products concerned which have, of course, already been licensed on the basis of their safety, quality and efficacy" *HSC 2002*

Patients in the RSS were not randomised between products. No attempt was undertaken to control for baseline characteristics between treatment cohorts, thus comparisons would be subject to selection bias and confounders between products. It is understood that some products were allocated to patients with low disease activity whilst others were reserved for those with higher disease activity. Merck cannot therefore support the use of the RSS data to compare outcomes of one product against another, or one product against the aggregate results of the scheme.

Merck also believe it is inappropriate to utilise a pooled result to assess individual products. Pooling implicitly assumes that the products have the same efficacy, contradicting findings from direct head to head studies and indirect analysis. Each product should be assessed through its individual target against Best Standard Care (BSC) as it was in the RSS and we should remain consistent with this approach.

Importantly, Merck wish to highlight that the prices assumed in the addendum for Rebif do not reflect the actual prices to the NHS per our agreement with the CMU. As such, ICERs are artificially inflated for Rebif and inaccurate.

Fundamentally, Merck would like to see all these products under this assessment retained within the NHS to allow patient choice, or market forces to determine their usage. As the RSS results and the majority of the parameters have been accepted by NICE, we hope that the Committee's conclusion will be the same.

1.1. Merck Model and NICE assumptions

Merck welcomes NICE's acceptance of the majority of the RSS model assumptions and the settling on the use of the RSS data for this technology appraisal. The RSS was designed to address the fundamental uncertainty around the long term efficacy of these products for the treatment of

persons with Multiple Sclerosis (MS). Merck feels that the recognition of the RSS results and use of this valuable real world evidence which involved thousands of patients is important.

In our submission, Merck kept closely to the principles of the scheme and the economic modelling and it was recognised in the Technical Assessment Group's (TAG) report that Merck's company submission "differed least" (section 14.4.10), from the DH. There are only three parameters where Merck differ from NICE's preferred assumptions; firstly in relation to the Annualised Relapse Rate (where we utilise clinical evidence from Rebif trials over the TAG's NMA), secondly Merck use the most accurate Rebif prices (as per agreement with the CMU, rather than list price) and thirdly in the use of Rebif's *individual* rather than pooled (the RSS aggregate) result. These differences are outlined in Table 1.

Table 1: Comparison of NICE preferred assumptions and Merck Submission

Assumptions	AG Addendum Assessment	Merck original submission
RSS data, supplemented by trial data. Only using the AG network meta-analyses where no RSS data exist such as Annualised Relapse Rate (ARR)	√	x (Merck used Rebif ARR from PRISIMS)
Including the assumption of treatment waning, (i.e. a 50% reduction in effectiveness after year 10 of treatment);	√	√
The DH approach to estimating backward transitions in the EDSS health states;	√	√
Use of discontinuation rates as in the AG model, that is, 5% discontinue treatment every year;	√	√
Including carers' disutilities.	√	√
Use of the current UK list prices for each drug	√	X (Merck used the Rebif prices available to the NHS since April 2016)
included a weighted average of both doses of IFN β-1a SC three times a week (Rebif), 44 and 22 µg, weighted by their use in the RSS	√	√
RSS Pooled (Aggregate) Hazard Ratio	√	X (Merck used the Rebif's Individual HR's from the 10 year RSS results)

Merck agrees with the majority of parameters NICE prefer, however, in terms of pricing assumptions and the use of the pooled disability progression result, we must disagree. We, would accept the use of the TAG's ARR results for Rebif as this was appropriately obtained through the NMA. The RSS was set up to assess individual products against their established target. It is not a robust use of the RSS data to pool efficacy results across the products (see Section 1.2). Additionally, NICE should now

have confirmation from the Department of Health (DH) of the CMU framework prices for Rebif which should be utilised when developing the guidance.

1.2. Utilising the pooled Hazard Ratio

Merck assumes that the attraction of utilising the pooled (aggregate) Hazard Ratio (HR) from the RSS is that it allows the opportunity to assess the Disease Modifying Therapies (DMTs) in their entirety and also provides for the inclusion of products such as Extavia and Plegridy without further evidence requirements.

However, implicit in pooling is a common efficacy assumption, which is not supported by the direct and indirect clinical evidence. Head to head studies such as EVIDENCE (Panitch et al 2002) find significant differences between the products. This was also highlighted in the recent conclusions from the Institute for Clinical and Economic Review (ICER) assessment of MS products in the US (ICER 2017)

Merck has a related opinion on the use of a pooled result and price (of all the DMTs; as is used in some analyses in the TAG's addendum). If the 'class'/ 'pool' of drugs is deemed cost-*ineffective*, all the products would either have to drop their prices proportionately, or certain individual companies would have to agree to adapt the price of their product for the benefit of the basket, whilst not being certain of the resulting impact on cost-effectiveness. The former process would demand pricing coordination, a principle which Merck would not entertain and the latter offers commercial uncertainty, which is unfeasible.

Perhaps in recognition of this, Warwick also present analyses using the pooled efficacy result to represent an individual drug's performance and that drug's individual company price. Merck feel that this too is inappropriate as it burdens the most effective products with a disproportional higher price impact than would be borne if they were assessed on their individual result. Merck sees this as fundamentally prejudicial and an unjust approach.

In conclusion, each product should be assessed using their individual RSS results and their actual NHS prices, versus BSC.

1.3. Rebif 22 & Rebif 44

Marketing Authorisation recommended dose of Rebif® is 44 mcg; the lower dose of 22 mcg is licensed for patients who cannot tolerate the higher dose in the view of the treating specialist. Merck present a principal analysis based on the weighted average of the numbers of patients recorded as taking the 44 and 22 mcg doses in the RSS, considered to be a reasonable reflection of these two doses in real life. We would like to welcome the fact that this is now reflected in the latest addendum and acknowledge TAG's agreement that this is the appropriate.

1.4. Rebif Prices

In terms of any assessment, we respect the fact that it is difficult for NICE to assess Commercial in Confidence (CIC) pricing agreements with full transparency.

Merck noted that the latest weighted average annual cost of DMTs under NHS prices was £8,000, and under list prices as £8,444. According to the addendum, Rebif's "'NHS price' following Y8 price changes" (Table 2: addendum) are used. From Merck's perspective, the prices for Rebif were higher at Year 8 than those now provided to the NHS. These prices may be different from Rebif's final End of Scheme prices and still overestimate the cost to the NHS.

Merck has been providing Rebif to the NHS at lower prices since April 2016 and has not only confirmed this through an End of Scheme Agreement with the DH, but has also provided the same prices in an agreement with the Commercial Medicines Unit (CMU). We understand that these documents have now been provided to NICE and reflect the relevant Rebif prices for this assessment.

It is apparent from Table 4 in the addendum that using the 'transparent NHS prices' and the treatment waning model, the ICER for Rebif v BSC is £39,600. However, from Merck's calculations, utilising the RSS result, the RSS model assumptions and Rebif's end of scheme prices (combined with other products transparent NHS prices), this cost per QALY decreases in line with the RSS threshold and meets the cost-effective criteria. It should be noted that Merck is unable to weight these prices proportionally across the RSS population.

1.5. Incremental analyses

In Merck's view, it is inappropriate to use the RSS data to draw comparisons between products, either implicitly, through pooling efficacy data (Section 1.2) or explicitly, through performing incremental analyses. The RSS was effectively an observational study and patients were not randomised between products. There was no attempt made to balance baseline characteristics between treatment cohorts, rendering any comparisons between them subject to selection bias. From clinician opinion, Merck believes that certain products were apportioned to patients with low disease activity whilst others were earmarked for those with higher disease activity. The distribution of these products across the RSS was not randomised. Therefore, it would be inappropriate to utilise this data to formulate any comparisons between products.

1.6. Patient Choice

Merck is firmly supportive of patient choice and believes that patients get the optimum out of their medication when the maximum number of options are available to them. The products assessed (as a response to NICE's original uncertainty) through the RSS have been determined, by independent assessment, to be effective over the long term. They now also have a considerable amount of published long term safety and efficacy data. It should also be observed that the maintenance of this patient choice is a low financial risk to the NHS. Persons with MS in the UK are only treated with one product at any one time. Therefore, there is no additional budget impact to the UK NHS in maintaining the availability of these products. All subsequent products assessed by NICE since 2001 have substantially larger list prices. The DMT's assessed through the RSS provide persons with MS an established treatment alternative to newer therapies.

Conclusion

Merck would like to reiterate its agreement with the TAG's original affirmation of the RSS analyses, which found the relevant DMTs in this appraisal to be cost-effective. The TAG have reported the MS Society's view, that "The range of treatment options allows for the differential way MS can affect individuals and their differential responses to DMTs." Merck continues to support this principle and encourages approval for all the DMT's being assessed, so that patient choice is maintained.

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Re: Novartis response to the Assessment Group Report Addendum for ID809: Multiple sclerosis - interferon beta, glatiramer acetate

Dear Mr Boysen,

Thank you for the opportunity to comment on the Assessment Group report addendum produced by Warwick Evidence as part of the multiple technology appraisal of interferon beta and glatiramer acetate for treating multiple sclerosis [ID809].

Having reviewed the report addendum, Novartis would like to comment on the inconsistency of references to Extavia®.

Extavia® and Betaferon® are considered to be the same drug (see Section 5.3.1 of the original Assessment Group report), and so Novartis kindly requests that both names are referred to where appropriate, when presenting results for 'IFN β-1b 250 µg every other day'. This would also ensure alignment with references to Plegridy® (like Extavia®, another intervention not included in the Risk Sharing Scheme). Novartis notes that 'Betaferon/Extavia' has been used in the addendum appendices (based on data from the Assessment Group's own review) and in the text of the report addendum (see page 13) when referring to inputs provided by the Department of Health, and kindly requests that this nomenclature is also used in the tables of the report addendum, where appropriate.

For consistency, Novartis additionally requests that the ordering of manufacturers reflects the order of the treatments presented in the report, i.e. 'Bayer/Novartis' rather than 'Novartis/Bayer' when referring to 'Betaferon/Extavia' (see page 13).

Finally, Novartis requests that the Assessment Group carefully checks Table 21 of the addendum, as the results presented do not appear to correspond with those generated by the version of the model released for consultation, whereas Tables 20, 22 and 34–36 do correspond.

Yours sincerely,

[redacted]

[redacted]

Teva response to Assessment Group Report *Addendum*

Teva welcomes the *Addendum* published by the Assessment Group (AG) and the resumption of the Appraisal process.

The primary point that Teva would like to raise is for Copaxone to be named consistently within the *Addendum*. As it currently stands, there is no reference to Copaxone 40mg three times weekly, and the 20mg dose of Copaxone is erroneously referred to as "*20mg SC three times weekly*" in a number of places (for details see Table at the end of this document). Teva, therefore, requests that both doses of Copaxone be referred to either as "*Copaxone 20mg once daily/40mg three times weekly*", in line with how "*IFN β-1a 44/22µg three times a week*" is referred to in the RRMS section of the *Addendum*, or simply as "*Copaxone*" with a note to recognise the two dosing regimens.

Teva would like to request greater transparency regarding the alternative disease state costs quoted by the AG. The source of these costs is unclear, as they are referenced to the natalizumab STA;[1] but, within this document, these costs are only referred to as being from the 'UK MS survey 2005/6' with no further details given of whether they have been formally published. These health state costs are considerably lower than others available in peer-reviewed publications (*e.g.* Tyas *et al*.[2] and Karampampa *et al*.[3]); hence, their providence and validity should be made clear.

It should be noted that the value of the pooled analysis of the DMTs is somewhat questionable, taking into consideration the wide range of list prices of the DMTs (from £6,701 to 10,572 *per* year) as well as the likely different efficacy profile across various beta-interferons. These differences in price can cause marked effects on cost-effectiveness, as shown by the AG calculations using pooled RSS efficacy data.

Teva welcomes the AG's considerations as to the most appropriate method to incorporate pegylated-interferon beta-1a (Plegridy) into this Appraisal. Teva agrees with the approach taken by the AG and the analysis conducted. Teva supports the AG's conclusion that assuming an equivalent efficacy for Plegridy and the beta-interferons is the most rational approach, based on the limited clinical evidence available for Plegridy.

Teva also notes that Copaxone is the most cost-effective option of these four first-line treatment options based on the ICERs in the *Addendum*.

The final area where Teva wishes to comment is in regard to the infrastructure contributions and their consideration during this Appraisal. It is noted that infrastructure contributions are not being included within the cost-effectiveness calculations for this Appraisal, despite being part of the

original scope, and Teva requests that a statement be included to make this clear. Such contributions provide direct financial support to the NHS and improve MS services, and should be recognised. Not including infrastructure contributions could be seen to set a precedent for future appraisals and may act as a disincentive for some manufacturers in the future. Teva would like to reaffirm their commitment to providing infrastructure contributions at their current level for the foreseeable future.

Additionally, looking beyond the *Addendum*, Teva wishes to highlight a relevant change in the Summary of Product Characteristics for Copaxone that has occurred during the course of this Appraisal. Copaxone is no longer contraindicated in pregnancy as summarised below:

- The previous inclusion of 'Pregnant women' in Section 4.3 has now been removed
- The following statement has been included in Section 4.6:
  'Studies in animals have not shown reproductive toxicity (see Section 5.3). Current data on pregnant women indicate no malformative or feto/neonatal toxicity of Copaxone. To date, no relevant epidemiological data are available. As a precautionary measure, it is preferable to avoid the use of Copaxone during pregnancy unless the benefit to the mother outweighs the risk to the foetus.'

Table: Errors within the AG Report *Addendum*

Location	Error/Issue	Correction
Table 2, p.9	20 mg SC three times weekly	Refer to both doses
Table 3, p.13	20 mg SC three times weekly	Refer to both doses
Table 4, p.13	20 mg SC three times weekly	Refer to both doses
Table 5, p.14	20 mg SC three times weekly	Refer to both doses
Table 6, p.14	20 mg SC three times weekly	Refer to both doses

References

[1] Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis. NICE, Technology appraisal guidance TA127, 2007. Available at http://www.nice.org.uk/guidance/ta127 [Accessed April 2017].
[2] Tyas D, Kerrigan J, Russell N & Nixon R. The distribution of the cost of multiple sclerosis in the UK: How do costs vary by illness severity? *Value Health* 2007; 10: 386-389.
[3] Karampampa K, Gustavsson A, Miltenburger C *et al*. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from the United Kingdom. *Mult Scler* 2012; 18: 41-45.

20 April 2017

Re: Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809] - Assessment Group's Addendum Report March 2017

Thank you for the opportunity to respond to the Assessment Group's additional analyses submitted in the Addendum Report.

The MS Trust's expertise lies in understanding and supporting the needs of people with MS and ensuring that people have access to effective treatments. Rather than make specific comments on the analyses carried out by the Assessment Group, we wish to draw the Committee's attention back to the aim of the MTA, as recorded in the final scope:

> In this appraisal NICE will appraise beta interferon and glatiramer acetate at their current NHS prices, and using additional data on long-term outcomes from the risk sharing scheme, to determine whether these technologies are now cost effective.

The original scope of the Risk Sharing Scheme (RSS) was to monitor the long-term effects of three beta interferons (Avonex, Betaferon and Rebif) and glatiramer acetate (Copaxone) in routine clinical practice and to compare each one individually against best supportive care to ensure ongoing cost effectiveness. There was no intention to compare one product within the scheme against another. We are concerned that increasingly complex analyses are using the data in ways for which it was not designed with potentially unreliable results. Direct comparison with drugs which were not part of the RSS, such as Plegridy, using clinical trial data obtained from a very different and, as far as we are able to establish, a very much smaller cohort of patients may also be misleading.

We wish to reiterate that the drugs being appraised are established treatments with well-defined safety profiles. MS teams are very experienced with these agents; there is a wealth of clinical experience confirming their general safety and well-established services to initiate and monitor treatment. The beta interferons and glatiramer acetate are of particular benefit to those who are risk averse and those who have a relatively low MS activity; for many people, their MS has remained stable while taking one of these drugs. Furthermore, they have continued to be an important treatment option despite the introduction of newer disease modifying drugs. We are aware that some people who switched from one of the injectable drugs to an oral treatment have subsequently switched back to an injectable drug. The availability of a range of treatment options accommodates the widest possible range of patient and clinician preferences, enhances patient adherence and, consequently, clinical effectiveness. The impact on patient care of withdrawing one or more of the beta interferons or glatiramer acetate should not be overlooked.

The beta interferons and glatiramer acetate are safe, effective and well-tolerated. The wealth of real-world experience of these agents has confirmed that at an individual patient level, different products will suit different individuals. Dosing schedules, storage, side-effects and tolerability will vary, so we stress that, having been shown to be clinically and cost-effective, **all these products should remain available as a treatment option for all eligible patients**.

Comments on ID809 addendum 4

[redacted] on behalf of the ABN

Comments of the documents:

1. The decision to assume equivalence of HR for Plegridy with other DMTs is reasonable, and avoids the otherwise unfairly favorable results which are based on extrapolating a one-year, modern era study and comparing this to extrapolated longer and older studies, creating apparent superiority in the absence of any valid head to head. If anything, assuming equivalence is, in itself, overly generous, given the brief pre-launch trialling
2. I note that relapse cost is not driving much of the modelling, as expected
3. The AG validate the RSS/DH calculations when using the same model, which is reassuring
4. Introducing carer disutility to the model counterintuitively increases the cost per ICER. It markedly reduces the QALY gain from BSC, but the drug effect above this new baseline is less marked.
5. The 2014/15 updated price/EDSS grade make the results less favorable, though I note the extremely non-linear nature of these, with a higher cost for EDSS 3 than 4 or 5, producing a perverse increase in cost for saving disability in the mid-range of the scale (more marked than older figures)
6. Overall impression is that the AG models are largely favorable, with GA coming out well, but with the others often still <£30k/QALY. RSS based models, which are more credible for the reasons well outlined, are less favorable, exceeding the £36k/QALY originally set
7. It should be recalled that when attempting to compare drugs within the RSS, that patients were not randomized among the drugs. The scheme was not designed to determine equivalent efficacy. While this has been assumed, in any effort to consider the drugs individually, prescribing habits in the era of RSS recruitment are likely to have unequally assigned more active patients to certain drugs.
8. There is little new to add to previous comments on the CIS results, except to highlight they are largely favorable, probably due to using the AG modelling throughout the RRMS phase
9. The difference between NHS price (pooled a £8000) and pooled list price, £8444, is highlighted. I note that in the "preferred assumptions" analysis, the higher price is used, and I do not see a version of this with the £8000 price. It is hard to judge the net affect of this without seeing the full workings of the model (p18)
10. Accepting the £8444 price, the aggregate cost/QALY in the preferred model is £44,300, with minimal chance of being <£30,000 in probabilistic models.

Discussion:

The result at face value appears to show the drugs are effective but, with the exception of GA, exceeding a cost-effectiveness threshold of £36k/QALY as originally targeted, and again with only GA coming in under £30k/ICER which seems to emerge as the target in these

documents. The conclusion of the RSS 10 year analysis as presented to date was that the drugs were on target to be cost-effective at £36000/QALY. In this more complex model, this aggregate cost per QALY does rise, though the absolute differences seen as a fraction of the total costs involved in treatment vs BSC are not large.

The analyses are very sensitive to assumptions on waning and the exact value of the hazard ratio applied.

It is hard to argue with the methodology and assumptions (except for use of list price rather than NHS price) which incorporate much of the advice given at the scoping meeting and subsequent NICE committee and recognize the contribution of the RSS to informing this review.

As commented in the response to the original analysis, this is an exercise quite divorced from current practice, based on drugs we use much less often, and based on results, both from the trials and the RSS, where treatment was started much later in the disease course and in an older population than would be the norm. I would thus regard this as a "worst case" scenario for the true value of these drugs in clinical practice. There is, perhaps, a hint of this in the more favorable costs/ICER seen in the CIS models vs the RRMS models.

These results fail to consider use of the drugs as part of a treatment strategy where only responders are left on treatment, with patients failing on treatment, as is currently the case, being rapidly escalated onto more effective therapies.

The efficacy of these drugs in reducing accumulation of disability in MS appears validated by the RSS results, incorporated in the analyses here. Many patients have benefitted over the last decade from the decision to adopt these therapies into the NHS, and perhaps even more so from next generation of drugs which build on this foundation. Debate about which of the figures presented should represent the "final answer" on the exact magnitude of this benefit, and thus any recommendation on drug availability, should not ignore the unique situation of performing this exercise retrospectively in a mature prescribing landscape.

As prescribing clinicians, we recognize the many factors that influence a patient's choice of any one therapy, and any decision to restrict choice based on cost at this stage would need careful consultation with patient groups to minimize the impact. In most centres, patients on this group are predominantly patients who have been stable on the drugs for several years or who have chosen them after tolerability problems with more modern drugs. Moving forward for newly diagnosed patients, the expanding treatment landscape of more potent therapies means these drugs will be initiated less often, and any disruption caused by restricting availability based on price would need to be balanced against the trend for the entire class to be declining in use.

MS RISK SHARING SCHEME FUNDERS' COMMENTS ON THE ASSESSMENT GROUP'S "ADDENDUM REPORT"

These comments are submitted by the Department of Health on behalf of the parties to the UK MS Risk Sharing Scheme, that is the Department and the four companies marketing the products covered by the scheme. We wish to comment on the use of incremental cost-effectiveness analysis in the Assessment Group's "Addendum report" and in particular on the variants using a class treatment effect.

NICE will recall that the 2002 MS Risk Sharing Scheme (RSS) was set up to ensure that each of the products covered by the scheme was cost effective when compared individually against best supportive care. The initial calculations took as given the estimates of treatment effects for the individual products derived by ScHARR from the pivotal RCTs. The monitoring component of the scheme then compared the observed disability progression for the patients on each product against the "target" expected for that product on the basis of the initial estimate of the treatment effect relating to disability progression. Where there was a significant discrepancy, the price of the product was adjusted to restore cost effectiveness at the threshold of £36,000 per QALY adopted for the purpose of the scheme. At the finally agreed RSS prices, following the final (year 10) analysis of the monitoring data, all 4 products (and the two doses of Rebif separately) were shown to be cost effective versus best supportive care when assessed with the model supplied to NICE. We regard it as important that patients with MS should continue to have as wide a choice as possible of effective disease modifying treatments, to allow for continuity of care for existing patients and variation between individual responsiveness for new patients.

The Risk Sharing Scheme was never intended as a basis for comparing one product within the scheme against another. We therefore believe that the use of RSS data for the purpose of a traditional incremental cost effectiveness analysis, in which the less apparently cost effective products are successively compared against the more cost effective products, is not appropriate. In particular, we think that the data are not robust enough either to confirm or to rebut the idea of a "class treatment effect", whether for all 4 products or for the 3 beta interferon products as a group. We would strongly urge NICE to use the RSS data only for the purpose for which it

was originally intended, ie to compare each product separately against best supportive care.

April 2017

Dear Jeremy

Re: NICE Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]

Sanofi Genzyme would like to thank the National Institute for Health and Care Excellence (NICE) for the opportunity to respond to the addendum 4 of the review of beta interferon and glatiramer acetate for treating multiple sclerosis. We would like to add that we are in agreement with the overall approach to the consideration of the evidence available.

We do have a few points that we would like to raise with the Committee, which are detailed below and relates to the modelling assumptions undertaken in the review.

1. **DMTs have no impact on backward transition**
   There is evidence that DMTs can lead to improvement in EDSS levels. A recent article published in Neurology (Giovannoni 2016) titled *"Alemtuzumab improves pre-existing disability in active relapsing-remitting MS patients"*, demonstrated that patient treated with alemtuzumab significantly had a 6-month confirmed disability improvement over 24 months. The authors state that *"the findings of EDSS improvement from baseline to month 24 in nearly half of the alemtuzumab treated patients, with improvements in all 7 EDSS functional domains, suggest that such disabilities may often be reversible (at least partially) in patients with active RRMS if they receive suitable therapy, irrespective of the type of baseline functional deficit. Favourable disability outcomes were not directly attributable to relapse suppression since, in the absence of early on-study relapse, EDSS scores improved in alemtuzumab-treated patients but deteriorated in those treated with SC IFN-b-1a"*. In addition, we believe that all recently evaluated DMTs have used the British Columbia (BCMS) dataset and included an improvement in disability due to DMTs. We would be grateful for the committee to consider this evidence and be consistent in their approach to this, and any future appraisals or reviews of DMTs in MS.

2. **Waning effect of 50% reduction in treatment effect applied after year 10**
   The waning effect applied for the interferons differs from previous technology appraisals, and most recently the daclizumab submission, which applied a 25% reduction after year 2 and 50% after year 5 to all comparators. We believe the same waning effect should be applied in this assessment as has been applied in previous assessments, for consistency of methodology.

3. **Implied hazard ratio**
   Although it has been acknowledged that the methodology used to estimate the implied hazard ratio leads to a ratio greater than the individual DMTs, as a manufacturer, we request greater clarity on the on the methodology used to calculate the implied hazard ratio, which would enable similar comparison to be made in future assessments.

Kind regards

[redacted]

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Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence: Addendum 5, incorporating errata to Addendum 4

Title: Clinical and cost-effectiveness of beta interferon and glatiramer acetate for treating multiple sclerosis

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Declared competing interests of the authors
The authors have no conflicts of interest.
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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

All CIC (Commercial in Confidence) data has been highlighted in blue and underlined, all AIC (Academic in Confidence) data is highlighted yellow and underlined

This report should be referenced as follows:

Contributions of authors

GJMT coordinated the project, led the review of clinical effectiveness and led the drafting of the report. PA led the review of cost effectiveness, the critique of the RSS submission and the economic modelling and contributed to drafting the report. XA co-led the review of clinical effectiveness and contributed to the drafting of the report. HM and JM contributed to the economic evaluation work and contributed to drafting the report. RC contributed to the reviews of clinical and cost effectiveness through search and information specialist support and to the drafting of the report. AK and SL contributed to the review of clinical effectiveness and to the drafting of the report. CC and OC contributed as clinical experts and to the drafting of the report. JP and JR contributed to the review of clinical effectiveness and to the drafting of the report. HF contributed to drafting the report. AC supervised the project and contributed to the drafting of the report.

Please refer to the International Committee of Medical Journal Editors (ICMJE) ***Uniform Requirements for Manuscripts Submitted to Biomedical Journals see*** http://www.icmje.org/

1. AG response to consultation comments

The AG thanks consultees for their comments on the addendum. We respond to the recurring issues arising in consultees' comments below.

Incremental analyses using RSS data

The AG acknowledges the challenges and limitations arising from an incremental analysis of drugs using the RSS data. In the original report, the AG recommended the RSS data be used as the base case primarily based on the pooled estimate of effectiveness for all on-scheme drugs, and did not prioritise an incremental analysis based on RSS data as a sensitivity analysis (instead using AG NMA results informed by randomised controlled trials). The AG provided an incremental analysis based on RSS data to support a broader picture of the results arising from the RSS and in response to requests from NICE.

Class effects for beta interferons

The AG acknowledges the diversity of views from consultees relating to the value of a class effect for beta interferons and for treatments in this appraisal more generally. The AG NMA did not support a consistent pattern of superiority of one drug over another on key clinical outcomes, and in particular between time to progression measured at 3 months and time to progression measured at 6 months. The AG received advice from clinical experts, including at the first appraisal committee meeting, that drugs considered in this appraisal could be considered as part of a class, though the AG also acknowledges the views of manufacturers relating to differential effectiveness of drugs. Both types of results are presented throughout. These specific analyses were undertaken at the request of the committee and of NICE.

Pricing of drugs arising from differences between prior agreements and current list prices

The AG acknowledges comments from consultees regarding the use of pricing schemes as opposed to current list prices. The AG took advice from the committee and from NICE that the only prices that could be meaningfully used for analysis were list prices, given the uncertain continuation of infrastructure contributions and other discounts arising from the RSS.

Assessing effectiveness of pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)

The AG acknowledges the diversity of views from consultees on how to best account for pegylated IFN β-1a 125 µg SC every two weeks (Plegridy) in this appraisal, given the committee's preference for RSS data, which do not include this drug. To further support decision-making, the AG has provided analyses using the AG NMA results for this drug as well as the committee's preferred assumptions.

2. Additional results relating to pegylated IFN β-1a 125 µg SC every two weeks

On request from colleagues at NICE, we have generated estimates relating to pegylated IFN β-1a 125 µg SC every two weeks (Plegridy) using a) AG estimates of annualised relapse rate and time to disability progression from network meta-analyses (NMA), documented in Table 1, and b) committee's preferred assumptions for all other relevant estimates. We present these findings both using AG state management costs and UK MS Survey costs. **We wish to stress that these results are not strictly comparable with results using RSS data given the different data sources used.**

Table 1: Findings from the AG NMA relating to pegylated IFN β-1a 125 µg SC every two weeks (Plegridy): time to disability progression confirmed at 3 and 6 months, and annualised relapse rate

Time to progression	Hazard ratio	Annualised relapse rate
Three months	0.62 (0.40,0.97)	0.64 (0.50, 0.83)
Six months	0.46 (0.26, 0.81)	

Using the results from the AG NMA on annualised relapse rate and time to disability progression confirmed at three months, in addition to the committee's preferred assumptions, pegylated IFN β-1a 125 µg SC every two weeks (Plegridy) compared to best supportive care was more costly and was expected to yield 1.729 more QALYs and had an ICER of approximately £10,500 per QALY gain (see Table 2). In Table 3 we present the results based on using the time to disability progression confirmed at six months. These results showed that pegylated IFN β-1a 125 µg SC every two weeks (Plegridy) was cheaper than best supportive care and yielded more QALYs, hence dominating best supportive care.

Table 2: Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy), using AG NMA data and the treatment waning model (time to progression confirmed at 3 months)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)	380,200	18,100	8.877	1.729	10,500
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 3: Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy), using AG NMA data and the treatment waning model (time to progression confirmed at 6 months)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)	360,100	-	9.707	-	-
Best supportive care	362,100	2000	7.148	-2.559	Dominated

ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years

We then replicated these analyses using costs from the UK MS Survey, as undertaken in the previous addendum. Using the results from the AG NMA on annualised relapse rate and time to disability progression confirmed at three months, in addition to the committee's preferred assumptions, pegylated IFN β-1a 125 µg SC every two weeks (Plegridy) compared to best supportive care was more costly and was expected to yield 1.729 more QALYs and had an ICER of approximately £25,900 per QALY gain (see Table 2). In Table 3 we present the results based on using the time to disability progression confirmed at six months. These results showed that pegylated IFN β-1a 125 µg SC every two weeks (Plegridy) was more costly than best supportive care and yielded more QALYs, with an ICER of approximately £14,500.

Table 4: Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy), using UK MS Survey costs, AG NMA data and the treatment waning model (time to progression confirmed at 3 months)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	225,700	-	7.148	-	-
Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)	270,500	44,800	8.877	1.729	25,900
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 5: Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy), using UK MS Survey costs, AG NMA data and the treatment waning model (time to progression confirmed at 6 months)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	225,700	-	7.148	-	-
Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)	262,700	37,000	9.707	2.559	14,500
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

3. Errata arising from Addendum 4

All table numbers are cross-referenced against Addendum 4 from this point.

Correct price for IFN β-1b 250 µg every other day (Betaferon/Extavia)

We thank consultees for detecting an error in the results presented for IFN β-1b 250 µg every other day (Betaferon/Extavia) in Table 21. These arose from an error in the price used. The correct results are presented below.

Table 1 IFN β-1b 250 µg every other day (Betaferon), using pooled RSS data and the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
IFN β-1b 250 µg every other day (Betaferon)	391,500	29,400	8.047	0.899	32,700
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Consistency of RSS parameters for glatiramer acetate 20 mg SC once daily (Copaxone)

Colleagues at NICE detected an inconsistency between pairwise analyses from RSS data and incremental analyses between glatiramer acetate and pooled beta interferons from RSS data, arising from differences in the values for RSS parameters used for glatiramer acetate 20 mg SC once daily (Copaxone). These arose due to slight discrepancies in the relapse rate ratios reported by the company for their RSS data and by the DH in their most recent communications with us. We used the RSS data presented by the DH for every other analysis in the report; thus, we provide below updated tables using the relapse ratio supplied by the DH ([redacted]).

Table 2 Scenario analysis results comparing beta interferons, glatiramer acetate 20 mg SC once daily on list prices using the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	362,100	-	7.148	-	-
Glatiramer acetate 20 mg SC once daily (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta interferons	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 3 Scenario analysis results comparing beta interferons, glatiramer acetate 20 mg SC once daily and using the treatment waning model and UK MS survey management costs

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	225,700	-	7.148	-	-
Glatiramer acetate 20 mg SC once daily (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta interferons	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]

Biogen Idec - New submission

Following the second appraisal committee meeting on 23rd May, NICE paused the appraisal for beta interferons (IFNs) and glatiramer acetate (GA) on the basis that several manufacturers were considering access agreements for their technologies, which means that the basis for the decision making would be subject to change. NICE shared a briefing paper with all manufacturers outlining the conclusions of the two previous appraisal committee meetings and presenting new plausible product specific ICERs based on the committee's preferred assumptions.

Biogen thank NICE for the opportunity to present a new submission for intramuscular (IM) IFNβ-1a 30µg (Avonex®) and subcutaneous (SC) pegylated IFN β-1a 125 µg (Plegridy®). Following this submission, NICE intend to go back to the appraisal committee, formulate draft recommendations and issue an appraisal consultation document.

Based on rationale outlined within the remainder of this submission, Biogen agree with the necessity for a public consultation for this appraisal, including input on the validity of assumptions and output of the cost-effectiveness model from the clinical and broader community.

Biogen are committed to work towards a solution that ensures continued access for all patients to IFNs and GA, however as stated in previous consultation responses, we also request the basis for decision making is made off sound and consistent grounds.

Biogen have two key concerns with the current preferred assumptions and economic model:

- The inappropriate use of the UK Risk Sharing Scheme (RSS) for non-scheme products and the pooling of its values based on the assumption of a class effect for the hazard ratio (HR) for confirmed disability progression (CDP), the most influential driver of cost-effectiveness, when individual treatment data are available
- The economic model used to estimate the most plausible ICER has not been quality checked or tested for face validity. Greater transparency in rationale underpinning assumptions and the model outcomes is warranted.

Biogen would welcome dialogue with NICE regarding our submission and concerns.

1) Assumption of class effect and use of RSS data

a. Inappropriate use of RSS data

Biogen would like to remind NICE of the importance in using the data accumulated from RSS appropriately, in accordance with the integrity of the study design and objectives.

The RSS was never designed as a cross-comparative study and should not be used as such to pool outcomes across treatments (as also cited by the Department of Health [DH] in response to

the prior addendum). It should be used solely as a mechanism to ensure that each product provides value to the NHS, as expressed in terms of the measures specifically designed for the purposes of the RSS.

Biogen's view on the use of the RSS data in the MTA can be supported by the DH final statistical report for IM IFNβ-1a 30µg where it was stated:

[redacted] (1).

The validity and applicability of the RSS data has also been questioned by UK clinicians, for instance in the BMJ editorial on the 6-year outcomes:

"There are limitations inherent to the nature of the project. This is not a randomised controlled trial and unrecognised biases may be driving the observed effect. Geographical, ethnic or temporal differences probably do not explain the divergence in the cohorts, but there may be unappreciated differences in patient selection or retention. It should be remembered, however, that this was not established as the definitive scientific trial on the long-term efficacy of disease-modifying therapies: it is a health policy initiative to determine, within acceptable margins, whether the NHS pays too much for multiple sclerosis drugs" (2).

The measures captured in the RSS do not lend themselves to a clear, comparative assessment of cost effectiveness as intended within this MTA:

- In the RSS, the main outcome measure was the change relative to baseline of a weighted sum of the proportions of patients who have progressed to each expanded disability status scale (EDSS) score; the weighting factors were loss of utility of patients in each EDSS, relative to the utility of 1 for perfect health. We question whether this outcome is the most robust and meaningful in efforts to clarify and quantify the value of disease modifying treatments (DMTs) to the NHS community;
- Modelling techniques have been used to construct a "virtual control group" against which the data from the scheme can be compared through the implied hazard ratio and deviation score. The natural history cohort of untreated patients used for comparison is from the British Columbia MS database.

It should be acknowledged that measurement of EDSS throughout the duration of the RSS was subjective dependent upon the assessor and did not include the validation with magnetic resonance imaging (MRI) as rigorously conducted in the blinded randomised controlled trials (RCTs).

MRI is now the most important tool for the diagnosis and monitoring of multiple sclerosis (MS) (3). Even in the absence of relapses, ongoing MRI activity indicates that pathological inflammatory activity continues to occur despite a lack of clinical symptoms (4, 5). MRI has become an essential tool for treatment monitoring, safety assessment in addition to predicting of disease progression (3).

A survey of UK neurologists with an interest in MS revealed 59% of respondents used MRI to monitor treatment response (6) and identify at-risk for progression of disability (7). To predict treatment response in terms of relapse rates and/or disability progression over 4 years, the

MAGNIMS study group recommends using the modified Rio Score which captures the change over the first year of new T2 lesions and relapses (8).

The McDonald criteria are now widely accepted and used to establish a diagnosis of MS. As understanding of MRI improved, the McDonald diagnostic criteria were introduced in 2001 and further refined in 2005 and 2010 (9). The McDonald criteria allow a diagnosis of MS to be made in a person who has had just one relapse, by incorporating evidence from MRI scans (9). Additionally, the EMA stated that MS may be defined as 'active' based on clinical and/or MRI evidence (9). This is not incorporated in the RSS.

Typical clinical MRI protocols currently include conventional sequences based on T1-weighted and T2-weighted imaging to identify and characterize disease pathology in MS (10). Recently, Kaunzner and Gauthier (3) provided a clear understanding of the link between MRI outcomes and the disease disability:

- Chronic T1-hypointense lesions are closely linked to neurodegeneration and are known to correlate with disability in patients with MS. A 10-year follow-up study showed that the number of T1 hypointensities at baseline and the increase in T1-hypointense lesion volumes predicted worsening EDSS. New or enlarging T1-hypointense lesion number and total lesion volume also correlated with EDSS change (11).

- An increased number of T2-hyperintense lesions and the higher lesion volume were associated with increased disability (12). The number of new T2-hyperintense lesions within the first 5 years was the strongest predictor of increased EDSS at 14 years and the follow-up study confirmed an association between early lesion accumulation and subsequent 20-year disability (13).

There is strong evidence for using MRI lesions as a predictor of relapses and disability progression from analyses and meta-analyses of data from clinical trials and real-world sources involving tens of thousands of people with MS. Consortium of MS Centres (CMSC) updated their recommendation to include brain MRI to demonstrate dissemination in time and ongoing clinically silent disease activity while on treatment, to evaluate unexpected clinical worsening, to re-assess the original diagnosis, and as a new baseline before starting or modifying therapy (14).

The Assessment Group (AG) report did itself acknowledge some additional limitations of using the RSS scheme:

- it is based on an observational design with a non-contemporaneous control cohort
- information from additional newer drugs could not be included to add to the robustness of the networks

Biogen would add that using the RSS data is further compromised by modelling techniques that rely on construction of a 'virtual control group' because of the omission of a control group representing best supportive care.

Justification for using the RSS data and not trial data was that the AG identified that 30 of 35 included RCTs were at high risk of bias. In some cases, results relied on sparse networks with uneven risk of bias throughout the network. They also cited that the short follow up times may not allow for adequate assessment of DMT effects.

However, the observational design used for the RSS will, by definition, be considered to be of lower quality of evidence in comparison to RCTs (which are seen as the "gold standard" (15) and preferred by NICE as noted in the Reference Case (16)). Therefore, this decision to use the RSS can only be based on follow-up time. Furthermore, it should also be acknowledged that all subsequent technology appraisals in relapsing remitting multiple sclerosis (RRMS) (e.g. (alemtuzumab, dimethyl fumarate) have used RCT-based evidence to inform decision making, despite this risk of bias.

In conclusion, there are major limitations in the design, outcome collection and analysis of the RSS. Biogen caution against over-interpretation or inappropriate use of this data source.

b. An unjustified class effect

'Class effect' is usually based on one of three definitions; similar chemical structure, similar biological mechanism or similar pharmacological effects (17, 18, 19, 20, 21). However the concept of 'class effect' was called a term of convenience that has never been defined by Furberg (22), and this lack of a consensus definition has led to varying interpretations (20, 22).

Drugs grouped into the same classes may still differ by structure, pharmacokinetics and mode of action and these differences translate into clinical practice in terms of both efficacy and tolerability. In addition, differences between individual patients in terms of their genetic or immunological profile, may trigger different responses to the same drug (18). Therefore, no two drugs are exactly the same and grouping them into a similar class requires many, often limiting, assumptions and risks a potential loss of important information about comparative benefits and harms.

As a minimum, assumptions of class effect should not be based on efficacy alone, but on the comparability of the safety profile as well(20). Drugs which have comparable efficacy may not have comparable safety profiles (17, 21).

Creating drug classes to facilitate a network (as in the RSS model) can make it difficult to draw conclusions about which is the most efficacious intervention, even at a class level (23). The number of interventions and trials within a class can vary substantially, which will impact the uncertainty and therefore the impact of the prior distributions on the variance parameters could be substantial, and use of extensive sensitivity analyses is crucial (23).

Misleading results can be generated when a class effect is assumed when none really exists. Because there is no standard definition of class effect and there are examples of instances where the assumptions of class effect have been shown not to hold, it is important for researchers to provide evidence in support of a class effect in each individual case where it is used. This evidence must include information about both efficacy and safety equivalence.

Where possible, the validity of the assumption of a class effect should be tested by comparing the results of analyses assuming a class effect with analyses based on separate drugs. Statistical testing for the heterogeneity of treatment effects across drugs in a class is not a particularly sensitive analysis and is only as robust as the power of the original (often) smaller studies. Thus, the lack of a statistically significant result from a test for heterogeneity does not necessarily exclude the presence of important variations in the response to different drugs (21).

With respect the current appraisal, the AG report concluded that IFNs and GA reduce relapse rate, reduce rate of severe relapses and generally delay disability progression. As one of the

results of their assessment of clinical effectiveness (paragraph 9.5.18), they drew the conclusion that:

'there was little evidence that any one drug was superior to others except for disability progression confirmed at 6 months, but networks were especially sparse'. They further stated that 'findings for discontinuations due to Adverse Events (AEs)…. did not suggest that one drug was more likely to result in discontinuation than another, or, with few exceptions, against placebo. However, findings for discontinuation relied on networks with some limited evidence of inconsistency'.

This assumed lack of difference between treatments helped form the rationale for using the RSS data in the cost effectiveness modelling. Furthermore, analysis of the RSS data produces one treatment effect for all DMTs thereby assuming a 'class effect' which, in our view, is not justified.

The assumption of class effect is not supported by the direct evidence presented in the AG report. For example, Figures 7, 11, 15 in the AG report all display pairwise meta-analyses (direct comparisons) of different drugs or different regimens of drugs. In each of these graphs (for different outcomes) there is evidence of significant differences in treatment effect, which is at odds with an assumption of class effect (data derived from EVIDENCE 2007, INCOMIN 2002 and PRISMS 1998 trials).

The supporting evidence for safety profile was also lacking and limited to 'discontinuations due to adverse events' alone as stated above. This provides further reason why a class effect assumption does not hold.

Furthermore, with respect to MRI outcomes, significant differences are apparent:

- IM IFNβ-1a 30µg vs SC IFN β-1b 250 µg: in the INCOMIN study, over 2 years, 55% of SC IFN β-1b 250 µg patients were free from new T2 lesions compared 26% of IM IFNβ-1a 30µg (relative risk of new T2 lesion 0.6; 0.45–0.8; p<0·0003) (24).
- IM IFN β-1a 30µg vs SC IFN β-1a 44 µg: MRI results from comparative phase of EVIDENCE showed that over a median duration of treatment of 62 weeks, 58% patients were free of new T2 lesions when receiving SC IFN β-1a 44 µg compared to 38% with IM IFN β-1a 30µg. The mean proportion of T2 activity scans in the two groups was 27% SC IFN β-1a 44 µg and 44% IM IFN β-1a 30µg (p<0.001) (25).
- SC IFN β-1b 250 µg vs GA 20 mg: In BEYOND, O'Connor et al. report a significant decrease was observed in T2 lesion volume from screening for patients in SC IFN β-1b 250 µg group compared with the patients in the GA 20 mg group at year 1 (approximately 0.4 cm3 in mean change in T2 volume for SC IFN β-1b vs approximately 0.8cm^3 GA 20 mg p=0.04) (26).

It is important that evidence to support the assumption of similar safety and efficacy profile is presented in each instance where class effect is used. It can reasonably be argued that this has not been done adequately in the current case. Head to head evidence should be provided to support any assumptions; evidence identified here does not support this.

c. SC pegylated IFN β-1a 125 µg long term data

In addition to the above and as described by Biogen in prior consultations, the outcomes of the RSS study should not be attributed to SC pegylated IFN β-1a 125 µg. The pivotal trial indicates

that SC pegylated IFN β-1a 125 µg has superior relapse rate reduction and disability progression data vs placebo (5). The maintenance of SC pegylated IFN β-1a 125 µg effect has also been clinically and radiologically proven (27).

In ATTAIN, the extension trial of ADVANCE, SC pegylated IFN β-1a 125 µg demonstrated a consistent, sustained effect on both clinical and radiological outcomes with long-term treatment.

- Efficacy and safety analyses of ATTAIN related to patients treated up to 3 years with SC pegylated IFN β-1a 125 µg were presented in Biogen's submission for the MTA [ID809] (section 3.3.2.4, pages 86 & 87). Information provided was from two posters presented at the 68th American Academy of Neurology (AAN) in 2016.
- In Fiore *et al.* (27), patients receiving continuous SC pegylated IFN β-1a (since Year 1 of the ADVANCE trial; n=376 ATTAIN intent-to-treat (ITT) population) continued to show low adjusted ARR into Year 6 and low mean number of MRI lesions (new T1, new/newly enlarging T2, Gd+) up to Year 4 .
    - In ADVANCE, patients treated with SC pegylated IFN β-1a had fewer and significantly smaller new or newly enlarging hyperintense lesions on T2-weighted images at 48 weeks (mean of 3.6 new or newly enlarging T2-weighted hyperintense lesions for SC pegylated IFN β-1a versus 10.9 for placebo, p<0·0001). SC pegylated IFN β-1a 125 µg patients had significantly fewer and smaller new T1 (mean of 1.8 T1 hypointense lesions at 1 year for SC pegylated IFN β-1a versus 3.8 for placebo, p<0·0001) (5).
- In Cui *et al.* (28), the safety and tolerability of SC pegylated IFN β-1a 125 µg remained favourable up to 5 years and there were no marked changes in event rates for any adverse events (AEs). The safety profile was consistent with that observed during the ADVANCE trial.
- In addition to these two posters, from Biogen's data on file (29), patients on SC pegylated IFN β-1a 125 µg since Year 1 of the ADVANCE trial continued to be associated with low CPM6M with 14% of the ATTAIN ITT population (n=376) with sustained disability progression at Year 6.

2) Model choice and inconsistencies

NICE's current approach to the modelling is to assume a class effect and use the real-world long-term data that are available for some of the drugs. Biogen believe these assumptions are to date, unjustified given RCT data and further clinical outcome differences (e.g. radiological and neutralising antibodies [NAbs]).

An alternate approach would be to not assume a class effect and base modelling of long-term cost-effectiveness on assumptions about the relationship between trial data (treatment specific short-term outcomes) and long-term outcomes from the real-world data (e.g. waning of effect). This is Biogen's preference as the methodology would be consistent will previous and ongoing Health Technology Appraisals (HTAs) for RRMS.

Biogen acknowledge that both approaches have flaws but would strongly urge NICE to reconsider the current approach for reasons previously outlined. Both sets of analyses should be performed to allow a comparison and deeper consideration of which has less bias or provide more relevant information for the decision making.

In the briefing paper to the manufacturers (July, 2017), the most plausible ICER of [redacted] was estimated using the economic model provided by the AG (option 1 above). Biogen had access to this model and were able to replicate this ICER with a small discrepancy [redacted]

Biogen would like to express concern on the validity of the model based on three observations:

- in the treated arm, patients are accruing the costs and effects of treatment beyond EDSS 7, overestimating drug acquisition costs and ultimately the ICER
- the application of waning is overestimated and inconsistent with more recent technology appraisals in MS
- the assumption for discontinuation lacks face validity. More than 40% of patients are assumed to still be on a DMT after 10 years which seems unlikely given emergence of higher efficacy DMTs and a general shift in the treatment landscape.

a. Overestimation of costs

As stated in the AG report, when describing the RSS model (paragraph 13.1.16 Treatment discontinuation), "*In the treatment arm of the economic model (…) treatment would be discontinued amongst individuals progressing to EDSS ≥7*". Therefore, only patients with an EDSS from 0 to 6 should be accruing the drug acquisition costs and effects of treatment.

Biogen have noticed that this stopping criterion (treatment discontinuation for EDSS ≥7) was not applied in the model. In the worksheet "States", costs and utilities associated with each EDSS level for treated states and untreated states are presented. Patients with an EDSS ≥ 7 in the "treated states" have their costs and utilities as if they received a treatment (cells K9 to M18), whereas they should accrue costs and utilities consistent with natural history or no treatment.

After updating the model to account for this stopping rule, the most plausible ICER using the same set of preferred assumptions from the committee was [redacted].

b. Overestimation of waning effect

In NICE briefing paper shared in July, the basis for the committees preferred assumption of a waning effect is from clinical expert opinion. Clinicians explained that the efficacy loss over time can be due to the development of NAbs or of resistance to treatment. It is to note that NAbs effect impact only IFNβ treatments (in vitro and in vivo data have shown that GA-reactive antibodies are not neutralising) (30). The impact on clinical efficacy of NAbs becomes apparent after 12-24 months (31). After 24 months on IFNβ treatment, patients who have not persistently developed NAbs will usually never develop them (32). The effect of NAbs only affects the efficacy of IFNβ therapies at an early stage of patients' treatment.

The proportions of patients developing NAbs amongst the IFNs are not the same. In the AG report, it was documented that a recently published systematic review of randomised trials, reporting results from up to 96 weeks , showed that 2.0%-18.9% for IM IFNβ -1a 30 µg, 16.5%–35.4% for SC IFNβ -1a 22 or 44 µg, and 27.3%–53.3% for SC IFNβ-1b 250 µg (Betaferon®) of patients developed NAbs (33). In contrast to these figures, 1% of patients developed persistent NAbs with SC pegylated IFN β-1a 125 µg, at year 2 of the ADVANCE trial (5). It is recommended that for patients who remain NAb positive, IFNβ therapy should be discontinued (34).

As stated in our submission to the preceding addendum (March 2017), aside from the correlations above, there is no published evidence to support the existence of a waning effect. The only documentation that does hint at a potential waning effect is derived from the RSS year 10 SAG report: [redacted] (35).

In the current model, the committee's preferred assumption is to apply a waning effect of 50% to the pooled RSS year 10 HR for CDP (HR 0.791 [0.771, 0.812]) from year 10 onwards. NICE has qualified the 50% reduction value as 'arbitrary' (briefing paper for this consultation, July 2017).

In contrast, in more recent technology appraisals for RRMS (alemtuzumab, dimethyl fumarate), also in the absence of evidence, NICE have implemented an assumption for waning to the magnitude of 25% at year 2 and 50% at year 5, applying this to CDP outcomes from network meta analyses (NMA) base on 2-3 year RCTs.

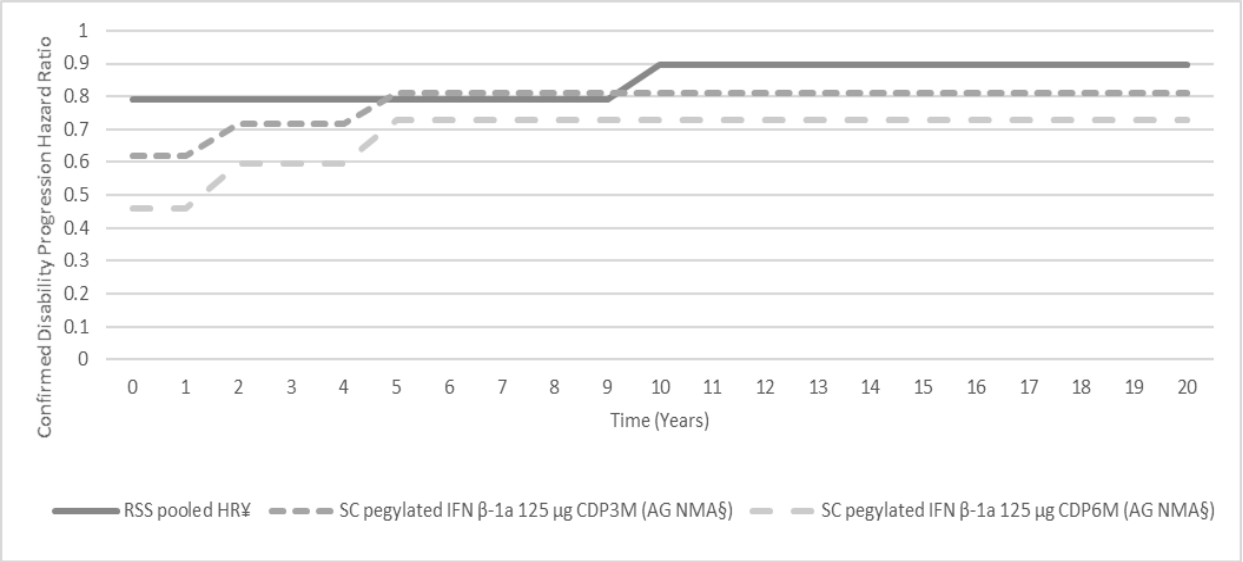
The application of waning in the current appraisal for the IFNs and GA is unfair comparative to more recent appraisals. The 50% reduction in year 10 onwards is applied to the year 10 pooled RSS HR which already factors in a degree of waning as noted in the SAG report.

In the case of SC pegylated IFN β-1a 125 µg, this underestimation of efficacy is exacerbated further with the HR for CDP being assumed to be equivalent to the pooled year 10 RSS data in addition to this arbitrary assumption of waning. Figure 1 illustrates the impact of current assumptions for SC pegylated IFN β-1a 125 µg with scenarios if methodology was reconciled fully with more recent technology appraisals. Table 1 outlines the consequences of these assumptions on the plausible ICERs.[1]

In these alternate scenarios and in particular for the CDP6M outcome (as preferred by the committee) SC pegylated IFN β-1a 125 µg is cost-effective and below acceptable willingness to pay thresholds.

[1] Using the original AG model: (ID809) MS - Aggregate Y10 base run with time-varying effect using AG assumptions UK MS EDSS costs - 050417 (noACIC).

Figure 1: Confirmed disability progression and waning scenarios for SC pegylated IFN β-1a 125 µg



¥ 50% waning year 10+
§ 25% waning at year 2 and 50% at year 5

Table 1: Plausible ICERs for the scenarios illustrated in Figure 1 for SC pegylated IFN β-1a 125 µg

Scenario	ICER (£/QALY)
RSS pooled HR¥	[redacted]
SC pegylated IFN β-1a 125 µg CDP3M (AG NMA§)	[redacted]
SC pegylated IFN β-1a 125 µg CDP6M (AG NMA§)	[redacted]

¥ 50% waning year 10+
§ 25% waning at year 2 and 50% at year 5

When the same alternate scenarios are used for IM IFN β-1a 30µg (Table 2), the ICER is lower in both scenarios with an important decrease when AG NMA CDP6M outcome is used.

Table 2: Plausible ICERs for the scenarios for IM IFN β-1a 30µg

Scenario	ICER (£/QALY)
RSS pooled HR¥	[redacted]
IM IFN β-1a 30µg CDP3M (AG NMA§)	[redacted]
IM IFN β-1a 30µg CDP6M (AG NMA§)	[redacted]

¥ 50% waning year 10+
§ 25% waning at year 2 and 50% at year 5

Biogen urge NICE to reconsider their preferred evidence source for comparative efficacy considering individual treatment data derived from the NMA (especially for treatments that were not included in the RSS) as opposed to making unfounded assumptions. Furthermore, Biogen request that arbitrary assumptions regarding the waning of effects are balanced and fair in comparison to more recent appraisals.

c. Underestimation of discontinuation

Biogen would also question the face validity of the annual discontinuation rates applied in the model. Currently this is based on an assumption of 5% as derived from the RSS observational data (for patient discontinuing due to AEs) with no differentiation between DMTs (Table 64,

p264 of the AG report). In reality, patients would discontinue treatment for a plethora of reasons beyond AEs, for example, lack of efficacy, adherence issues, planning a pregnancy or patient preference. The AG report highlights in its report the uncertainty around the discontinuation data stating page 216 that "*there is little evidence to support this [5%] assumption*".

Using the current model assumptions, 4,217 patients are assumed to start treatment at year 0. After 10 years 1,907 patients are estimated to still be on treatment (45%).[2] Biogen believe that this is an overestimation of clinical practice reality today, especially given the emergence of higher efficacy therapies from 2007 onwards.

Biogen would urge NICE to reconsider the current assumptions around discontinuations to ensure the model outcomes have a degree of face validity. In the latest technology appraisal in MS appraisal (TA441), annual discontinuations of 9.9% for IM IFN β-1a 30µg (24, 25, 36, 37) and 10.4% for SC pegylated IFN β-1a 125 µg (38) have been used and accepted by the committee.

With an annual discontinuation of 10% each year, 26% of patients would still be on treatment after 10 years (1,111 over the 4,217 initially treated).

Conclusion

Biogen, alongside NICE and other participating manufacturers are committed to work towards a solution that ensures continued access for patients to IFNs and GA.

NICE have explicitly stated on several occasions their preference for price realignment amongst these therapies. In light of this new submission and the critical issues raised, Biogen agree with the necessity for a public consultation for this appraisal, including input on the validity of assumptions and output of the cost-effectiveness model from the clinical and broader community. Following consensus, Biogen are willing to consider access agreements for our included technologies.

[2] Using the original AG model: (ID809) MS - Aggregate Y10 base run with time-varying effect using AG assumptions UK MS EDSS costs - 050417 (noACIC).

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Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]

Merck's response to NICE's invitation for a further submission post-second ACM

Executive Summary

Merck would like to acknowledge the ambition we share with NICE to work towards a solution in this appraisal that ensures that patients and physicians continue to have access to the current complement of treatment options for multiple sclerosis. We have been notified of the Committee's preferred assumptions in the Rebif® analysis and subsequently requested a copy of the TAG's economic model. We use this model in all present estimations to ensure full consistency with the Committee's view of the economics.

As previously raised, Merck views the pooling of RSS effectiveness results for the individual products, rather than the use of each drug's individual RSS result, as an inappropriate use of the RSS data. Not only does the assumption of comparable efficacy contradict findings from direct head to head studies and indirect analyses, the RSS was never set up to be used in this way. Selection bias is a real concern and no attempt has been made to adjust for differences in baseline characteristics between patients treated with the individual RSS products. Merck cannot recall an example of where NICE has accepted a naïve pooling of observational data as a basis for efficacy assumptions. Importantly, this approach is prejudicial against the more effective products who will bear a disproportionally higher price impact than would be borne if they were assessed using their individual RSS result. We propose that the assessment for all DMDs be based on their individual RSS hazard ratios.

The Committee have elected to utilise a more contemporary approach to costing EDSS states, utilising the source (UK MS Survey) that has been used in several recent prior HTAs. Merck agrees this is appropriate. Consistent with it, we propose that a more contemporary approach to mortality is adopted. Specifically, we apply an EDSS-dependent mortality multiplier, from Pokorski (1997), to estimate MS mortality from UK general population rates (sourced from ONS data for 2012-2014). This approach has been used in recent MS appraisals, TA254, TA303, TA312 and TA441 and avoids the application of an arbitrary standard mortality multiplier across all states and the potential double counting of mortality effects (which the TAG were concerned exists in the RSS's original approach to mortality). We have adapted the TAG's economic model to incorporate this functionality in order that it can be applied across all drugs in this MTA.

In summary and in response to NICE's invitation for this further submission, we:

- Propose a revision to the price for Rebif® (submitted to the DH) and consequently reduce the annual costs that are assumed in the economic model
- Provide an argument against the Committee's preferred assumption to pool the efficacy results for all products from the RSS
- Propose the Committee utilise a more contemporary approach to their assumptions mortality, one which is consistent with what has been done in prior appraisals
- As requested, provide a scenario which aligns with the Committees stated preferred assumptions (where the ICER for Rebif® v BSC at Rebif®'s revised price is [redacted]) and a second which incorporates assumptions that Merck believe are more reasonable and which

should form the base case for decision making about Rebif® and all other medicines in this MTA (where the ICER for Rebif® v BSC is [redacted]).

- Provide functionality within the TAG model which will allow the revised assumption relating to mortality to be implemented (so that it can be applied across all medicines in this MTA, not just to Rebif®).

In conclusion, Merck have submitted a reasonable economic analysis which demonstrates that Rebif® is a cost-effective treatment for patients with MS. It is important that there is a sustained funding mechanism for people with multiple sclerosis to continue to have access to Rebif® as part of a range of DMTs from which they and their physicians can choose. Reflecting widespread opinion, the Association of British Neurologists guideline states that: "It is essential that MS specialist neurologists can prescribe the full range of available licensed treatments according to what is clinically appropriate and best meets individual needs."

1. Committee's preferred assumptions

The following are stated as the Committee's preferred assumptions in their assessment of Rebif®. We use these as the basis for our response.

- To apply treatment 'waning' through a 50% reduction in efficacy after year 10
- To use the relative relapse and discontinuation rates as in the assessment group's model
- To apply UK list prices for each drug (unless a formal Patient Access Scheme or agreed Commercial Medicines Unit price is available)
- To include the disutility to carers
- To use the pooled RSS effectiveness data for all of the treatments in this appraisal
- To accept that the UK MS Survey was the most appropriate source for EDSS health-state costs
- To assume the proportion of people taking each dose of Rebif® (i.e. 22mcg and 44mcg) is the same as observed in the RSS

2. Revision to Rebif® price

In response to NICE's invitation for a further submission, Merck have submitted a revised discount to the Department of Health for Rebif®. Table 1 presents the revised annual price of Rebif® to replace the current prices in the economic modelling.

Table 1: Annual costs of Rebif® in economic model

Dose	At list price	Current price	New proposed prices
44mcg	£10,572	[redacted]	[redacted]
22mcg	£7,976	[redacted]	[redacted]
	Proposed discount from list of →		[redacted]

*Submitted to the Department of Health

3. Pooling of HR to represent efficacy

Merck continues to view the TAG's use of pooled RSS HRs across all products as an inappropriate way to use the RSS data. This is being proposed as the basis of the efficacy assumption for all DMTs in the MTA. We encourage the Committee to revisit this assumption for the following reasons:

- Patients in the RSS were not randomised to the products they received and it is highly likely that baseline differences between the different patient cohorts will result in bias if they are naively pooled. In fact, clinical experts have suggested in this appraisal process that some products were allocated to patients with low disease activity whilst others were reserved for those with higher disease activity. Merck cannot recall another example from an appraisal where NICE has accepted naïve pooling of observational data to inform assumptions of (comparable) efficacy.
- Pooling implicitly assumes that the products have the same efficacy, contradicting findings from direct head to head studies and indirect analysis. Head to head studies

such as EVIDENCE (Panitch et al 2002) find significant differences between the products. This conclusion has also been highlighted by the Institute for Clinical and Economic Review (ICER) assessment of MS products in the US (ICER 2017). Merck is aware from the briefing received from NICE that the Committee has heard from clinical experts that the drugs under appraisal are considered to be 'broadly similar' in clinical effectiveness. [redacted] Merck can provide more detail about this marketing study if required; the purpose of describing it is to highlight that there are a range of clinical opinions available.

- Even if the drugs are considered to be 'comparable', it seems to Merck that use of a 'pooled' measure of effectiveness represents a departure from NICE's usual preference to use the point estimates from comparative analyses in the models.
- Additionally, the move to using a pooled HR affects the individual drugs differently. The more effective products (those with lower individual RSS HRs) are prejudiced against and consequently require a disproportionally higher price adjustment to meet a cost-effectiveness threshold than would be required if they were assessed using their individual RSS result.

In conclusion, Merck's view is that each product in this MTA should be assessed using their individual RSS results and their actual NHS prices, versus BSC.

4. Merck's alternative proposal for mortality assumptions

The RSS model incorporated mortality in two ways. An assumed standardised mortality ratio of 2.00 was applied to general life table mortality estimates for all patients. In addition specific MS related mortality rates based on the ScHARR model were applied to EDSS levels 6 and above. The TAG was concerned that this theoretically led to double-counting of MS-related deaths in the model because they felt that MS-related death is already captured in the transition matrices. Subsequently they changed the risk of MS-related death to the same as that for the general population. In the TAG report, Warwick notes that an alternative approach that was not explored "would have been to consider using mortality multipliers for lower EDSS levels to capture the increased risk of mortality for those with MS compared to the general population".

Merck believe that the TAG's alternative approach is reflected by the mortality assumptions made in several recent MS submissions to NICE (TA254, TA303, TA312 and TA441), i.e. the application of mortality multipliers (reported by Pokorski et al, 1997) to age- and gender-specific all-cause mortality risks for the general population in each EDSS state. This is the approach that Merck presented in our original NICE submission and given its use in prior appraisals and the fact that conceptually it results in a more accurate profile of mortality risk across EDSS states than the application of a single SMR across them all, we propose that this method is applied in the base case (for all DMTs in this MTA).

We have provided transparent functionality within the TAG model to enable this to be adopted across the board. Box 1 below provides an overview of the changes Merck has made to the TAG model.

Box 1: Amends proposed to TAG model

The ERG has alluded to the possibility of including mortality in the model in line with previous appraisals, and as included in the Merck submission (sensitivity analysis). The Assessment Group model supplied during the course of the Appraisal was adapted to allow this feature to be applied in that model, with clear reconciliation to the Assessment Group's (AG) most recent base case (for the Rebif analysis).

A model option cell (mort.option) was added that takes the value 'Sheffield' for the current AG preferred based case and 'Pokorski' for the SMR option. Note the SMR cell in the Control sheet is unaffected. When Pokorski is selected this modifies the Natural History and On Treatment transition matrices to replace the Sheffield EDSS mortality rates with those based on application of EDSS specific SMRs to population life table rates. A macro is applied to run the model cycle by cycle.

In modifying the model to this end, we also added a second Results sheet (rather than modifying the original) that replicates the results in the original, but records these for both Rebif® doses. A weighted average set of results is then displayed. Note that a Macro is required to update the analysis.

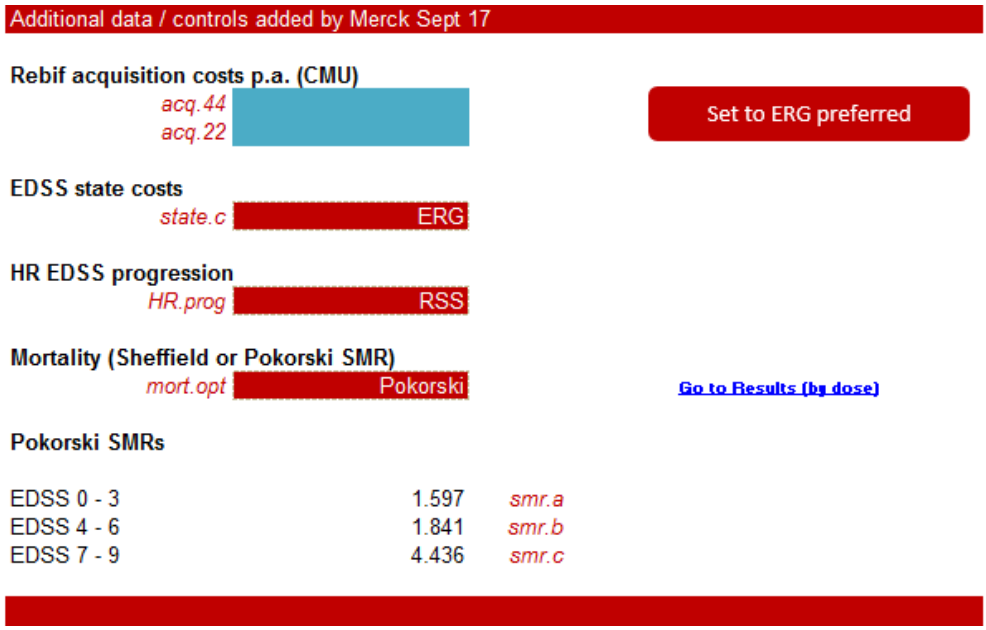
We also added:

- a switch between the Assessment Group model EDSS costs and those in the Merck submission (updated RSS model costs)

- a switch between the Pooled hazard ratio for progression and the specific RSS results for Rebif

The modifications to the model were kept to a minimum and a macro to set the model to the ERG's preferred base case is included.

Extract from Control panel sheet



5. Results (with revised Rebif® prices)

In both of these scenarios we implement the Committee's preferred EDSS health state costs (set at 2014/2015 prices); we have not inflated them to the current year and as such they may be a slight underestimate of today's costs (slight overestimation of the ICERs in each scenario).

5.1. Scenario 1 (TAG base case)

The results of the cost-effectiveness analysis of Rebif® versus BSC applying the Committee's ` preferred assumptions and the revised Rebif® prices are presented below in Table 2.

Table 2: Cost-effectiveness of Rebif® versus BSC with Committee's base case assumptions

Rebif 44mcg and 22mcg (in observed proportions from RSS)	Average per patient		
	Cost	QALYs	Cost/QALY
Drug costs	[redacted]		
State costs	[redacted]		
Relapse costs	[redacted]		
Active treatment	[redacted]	8.047	
State costs	[redacted]		
Relapse costs	[redacted]		
No Treatment	[redacted]	**7.148**	
Drug costs	[redacted]		
Cost offsets	[redacted]		
Marginal vs no treatment	[redacted]	0.899	[redacted]

5.2. Scenario 2 (Merck base case)

The results of the cost-effectiveness analysis of Rebif® versus BSC applying Merck's base case assumptions (differing from the Committee's in that we use Rebif's individual RSS HR and apply Pokorski mortality estimates to EDSS health states), alongside the revised Rebif® prices are presented below in Table 3.

Table 3: Cost-effectiveness of Rebif® versus BSC with Merck's base case assumptions

Rebif 44mcg and 22mcg (in observed proportions from RSS)	Average per patient		
	Cost	QALYs	Cost/QALY
Drug costs	[redacted]		
State costs	[redacted]		
Relapse costs	[redacted]		
Active treatment	[redacted]	7.902	
State costs	[redacted]		
Relapse costs	[redacted]		
No Treatment	[redacted]	**6.902**	
Drug costs	[redacted]		
Cost offsets	[redacted]		
Marginal vs no treatment	[redacted]	1.000	[redacted]

Response to the July 2017 correspondence from NICE

Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]

TEVA UK LIMITED

September 2017

Executive Summary

Teva welcomes the opportunity to comment on the letter received from NICE on 07 July 2017 setting out the preliminary conclusions of the appraisal committee ("Appraisal"). This response summarises our concerns about the procedure followed in this MTA and the committee's initial preferred assumptions and includes an updated version of the Teva base case analysis.

Teva has particular concerns with the justification and validity behind some of the committee's preferred assumptions, namely:

- The use of pooled Risk Sharing Scheme (RSS) effectiveness data for all treatments and the associated assumption of a class effect between Copaxone and the beta interferons
- The use of the UK multiple sclerosis (MS) Survey 2005/6 as the source for Expanded Disability Status Scale (EDSS) health-state costs
- The drug prices used and the subsequent disregard for MS infrastructure contributions

The principal concern of Teva surrounds the assumption of a class effect between Copaxone and the beta interferons and the resulting conclusion that the RSS data for all four disease modifying treatments (DMTs) could be pooled. The committee gave three reasons for its preliminary determination in this respect: (a) that the network meta-analysis (NMA) did not demonstrate material differences between the treatments; (b) that the data from the RSS were potentially subject to selection bias; and (c) the analyses of individual DMTs in the RSS excluded patients who switched to a different treatment, and these patients may have a worse prognosis than those who do not switch. Teva strongly believes that the committee's conclusions in this respect are scientifically invalid and patently unreasonable.

Firstly, there is no scientific basis for assuming a class effect between all four DMTs:

- Copaxone has a distinct chemical structure which bears no similarity to the structure of the beta interferons
- Copaxone has mechanisms of action which are different to those of the beta interferons
- Copaxone treatment results in specific clinical effects, as shown by its adverse event profile and, in contrast to beta interferons, a lack of development of neutralising antibodies
- Copaxone is no longer contraindicated in pregnant women, which is important given that many MS patients are women of child-bearing age
- There has never been any suggestion, whether by NICE in the context of the previous appraisal of DMTs or in any other context of which Teva is aware, that it is appropriate to assume a class effect between DMTs or to pool data to obtain a common estimate of effectiveness applicable to all treatments
- There is no credible evidence from randomised clinical trials to prove equivalence in efficacy between Copaxone and beta interferons
    - The NMA is stated as the primary support for assuming equivalence, but there is a high degree of heterogeneity in the clinical trial data on which it is based and a sparse network of evidence for key results
    - The results for the DMTs vary considerably in the NMA, albeit there is overlap in the confidence intervals – *e.g.* the rate ratios for relapse *vs* placebo varied from 0.60 to 0.77 across the DMTs
    - Evidence from comparative, randomised clinical trials suggest a benefit for Copaxone over the beta interferons

- The real-world evidence from the RSS supports a conclusion that Copaxone has potential efficacy advantages in terms of disability progression:
    - These data were strong enough to form the basis for an application by Teva for a Type II variation to include these beneficial effects on disability progression within the Summary of Product Characteristics (SmPC) of Copaxone
    - Far from concluding that the data for the different DMTs showed comparable efficacy, Copaxone was the only one of the four treatments where actual benefits observed in the Scheme exceeded predicted benefits, with the result that Copaxone was the only one of the products granted an increase in price following analysis of data

Secondly, the committee's concern that the data obtained from the RSS are potentially subject to selection bias is speculative and does not justify a conclusion of a class effect between DMTs or pooling of data. The RSS was designed and established by the Department of Health to provide real world evidence of the benefits of DMTs, building on the results of the original NICE appraisal of these treatments. The resulting data have provided such evidence and represents the most reliable evidence for these treatments. Overall, none of the apparent weaknesses in the RSS is sufficient to justify disregarding the differential benefits associated with the four DMTs demonstrated in the Scheme and provides no scientific validity to an assumption of a class effect in the context of the differences between the products identified above.

The arbitrary assumption of a class effect and the committee's decision to pool data for all DMTs simply acts to dilute the benefits of Copaxone and adversely to impact the cost-effectiveness analysis carried out in relation to Copaxone in this Appraisal. This reduces the credibility of the conclusions overall. The pooling of data for the DMTs also prevents a comparative cost-benefit consideration of these treatments, which is highly relevant to current clinical practice. The clinical decision made by treating neurologists is which DMT to prescribe a patient, not whether to use a DMT or best supportive care (BSC).

The other main area of concern for Teva is the heath state costs used in the Appraisal as:

- The committee's preferred source for costs has never been published in a peer-reviewed journal (in the form as it is used in the Appraisal) and there is, therefore, a lack of transparency into how the costs have been derived as this has not been made available to Teva
- Previous NICE appraisals have raised a number of weaknesses within these data, such as a low response rate (16%) with few patients from low and high EDSS states, being potentially unrepresentative of MS patients in general, being unpublished, and concerns over the methods of extrapolation employed (Evidence Review Group comments from the natalizumab single technology appraisal [STA])
- The committee has failed to consider the uncertainty in health state cost figures, with the probabilistic sensitivity analysis conducted by the AG not reflecting the true variation in health state costs
- The committee has not used costs adjusted for inflation
- The committee has excluded informal care from its consideration despite carer's disutilities being included. In a chronic and progressive condition such as MS, without informal care the costs to NHS/PSS (personal social services) would be significantly higher and so this should be considered

Teva also believes that the stance that NICE has taken regarding infrastructure contributions, as part of their consideration of drug prices to be used in this Appraisal, is inappropriate and inconsistent with the Scope of this Appraisal. These contributions, which are part of formal agreements that accompany the supply of Copaxone and other DMTs, are an intrinsic part of the service delivery pathway for these DMTs and have transformed MS care within the UK. They therefore provide a clear benefit to patients and the NHS that is not captured within the current ICER calculations. The availability of such contributions results in cost savings to the NHS and was, therefore, included within the scope for this Appraisal. The committee has chosen to disregard them on the basis that "they do not match modern funding pathways". This statement is unexplained in the letter of 07 July 2017.

In general, Teva has concerns regarding the apparent unfairness in the approach of the committee to this Appraisal. The assumptions favoured by the committee are extreme and not supported by evidence. The overall effect is artificially to increase the ICER values for Copaxone, in particular. Such an approach is neither fair nor reasonable, and contrasts to the recently published AG report that shows Copaxone to be a cost-effective treatment (published in the journal Health Technology Assessment in September 2017). Teva strongly believes that the most fair and justified assumptions to use in an updated base case analysis would be to:

- Use the Copaxone specific effectiveness data from the RSS (alongside the Copaxone specific population data)
- Use the average costs of the RSS and UK MS survey 2005/6 costs (both inflated to 2015/16 levels), in recognition of and in order to mitigate the weakness of the available health state cost estimates, with it being most likely that the true health state costs lie between these estimates
- Include a consideration of the infrastructure contributions in the drug price which is fair and appropriate (*i.e.* in the manner agreed for the RSS, where a discount of [redacted] *per* annum is applied)

The use of these assumptions in the model supplied by NICE (with no changes to other assumptions/parts of the model) produced an ICER value of £[redacted] for Copaxone *vs* BSC. The Table below demonstrates how each amendment to the committee's preferred assumptions impacts the ICER.

Comparison of ICERs under various assumptions and in the updated Teva base case analysis

Scenario	ICER for Copaxone *vs* BSC
Committee preferred assumptions – correspondence 07 July 2017	£[redacted]
Use of Copaxone specific effectiveness (& population) data from RSS	£[redacted]
Use of Copaxone specific effectiveness (& population) data from RSS and average costs of RSS and UK MS survey inflated to 2015/16	£[redacted]
Updated Teva base case (Copaxone specific effectiveness from RSS, averaged health state costs and infrastructure contribution consideration)	£[redacted]

In a scenario analysis that uses health state costs as those in the UK MS survey (committee preferred), the ICER is £[redacted], while the use of health state costs from the RSS model results in an ICER of £[redacted]. Considering the updated Teva base case and assumptions, we would ask the committee to re-assess the cost-effectiveness of Copaxone as a first-line treatment of relapsing forms of MS.

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List of Abbreviations

AG	Assessment Group
BEYOND	Betaferon efficacy yielding outcomes of a new dose
BSC	best supportive care
CIS	clinically isolated syndrome
CNS	central nervous system
CombiRx	combination therapy in patients with relapsing-remitting multiple sclerosis
DMT	disease modifying treatment
EDSS	Expanded Disability Status Scale
FAD	final appraisal determination
GA	glatiramer acetate
HCHS	Hospital and Community Health Services
ICER	incremental cost-effectiveness ratio
IFNAR	interferon-α/β receptor
ISR	injection site reaction
MBP	myelin basic protein
MHC	major histocompatibility complex
MMP	matrix metalloproteinase
MS	multiple sclerosis
NBCD	non-biological complex drug
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
PAS	Patient Access Scheme
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life year
REGARD	Rebif® *vs* glatiramer acetate in relapsing multiple sclerosis disease
RSS	Risk Sharing Scheme
SIPR	systemic immediate post-injection reaction
SmPC	Summary of Product Characteristics
STA	single technology appraisal
UK	United Kingdom

1. Assumption of a class effect

Under the committee's preferred assumptions, pooled Risk Sharing Scheme (RSS) data were used as the source for efficacy data on disability progression. Teva fundamentally disagrees with the justification and validity of the assumption of a class effect.

Teva is also surprised by the sudden change in direction in this area following the 2nd committee meeting. In the slides presented at the 2nd committee meeting, the potential class effect for interferons was outlined as an area to be discussed, with the beta interferons pooled whilst keeping Copaxone separate. There was no indication that a class effect including Copaxone was to be considered. Previously, throughout the Assessment Group (AG) report, Copaxone has been considered separately from beta interferons in almost all analyses. There were even specific analyses of the RSS data conducted using pooled beta interferon data and separate Copaxone data within Addendum 4. The sudden change to considering a class effect across all treatments, therefore, was totally unexpected.

In the correspondence supplied by NICE in July 2017, the committee's rationale for this decision is presented as being for the following reasons:

- "*Although glatiramer acetate has a different mechanism of action from beta interferons, the committee noted that the network meta-analysis results did not show that any particular beta interferon or glatiramer acetate was better than another*."
- "*Data for each individual technology in the RSS could be subject to selection bias. That is, because people in the RSS were not randomised to a specific treatment, the treatment decision, and therefore the outcomes, may have been affected by differences in the patient characteristics*."
- "*The pooled analysis from the RSS included people who switched to another treatment, whereas such people were excluded from the analyses for individual treatments. The committee considered that, although few people switched treatments, people who do switch may have a worse prognosis than those who do not. This means that the hazard ratios are lower (that is, the treatments appear more effective) in the analyses for the individual treatments than in the pooled analysis*."

Teva finds that whilst these potential justifications for an assumption of a class effect may be reasonable for the beta interferons, they do not provide any scientific justification for such an assumption regarding Copaxone. This view is due to distinct differences between Copaxone and the beta interferons, as well as weakness in the other reasons used by the committee to justify this assumption. Evidence in the following areas will be provided to demonstrate that Copaxone cannot be assumed to have clinical equivalence with the beta interferons:

- Chemical structure and mechanism of action
- Distinctiveness of clinical characteristics
- Evidence from clinical studies
- Characteristics of the RSS
- Comparators

The following sections outline the arguments in each of these areas.

1.1 Chemical structure and mechanism of action

Copaxone is a totally distinct chemical entity from beta interferons and the available evidence, recognised by the committee, shows that it has an entirely different mechanism of action. The following quotes regarding the chemical structure and mechanism of action are taken from the original submission by Teva for this Appraisal:

"*Copaxone is classified as a non-biological complex drug (NBCD) and is a complex heterogeneous mix of polymers composed of four amino acids: L-glutamic acid, L-lysine, L-alanine and L-tyrosine.*[1,2] *The amino acids are present in the polymer chain at a molar ratio that mimics myelin basic protein (MBP). The polymers contain an almost incalculably large number of amino acid sequences (with more than* $1x10^{36}$ *possible sequence combinations).*[3] *The constituents of individual chains and the concentration of chains of different lengths is a product of the unique manufacturing methods employed by Teva Pharmaceuticals, which are patented (until 2025) and would be difficult to replicate*."

"*Copaxone has a proposed mechanism of action that is distinct from that of other DMTs [disease modifying treatments]. The exact mechanism by which Copaxone exerts its therapeutic effects is not fully understood. However, it is thought to act by modifying immune processes that are currently believed to be responsible for the pathogenesis of MS [multiple sclerosis].*[1,2] *Animal studies have suggested that Copaxone induces the central production of anti-inflammatory and regulatory Th2 cells (a white blood cell subtype).*[4] *Th2 cells can produce anti-inflammatory and neuroprotective effects within the central nervous system (CNS) in animal studies.*[4] *This contrasts to beta interferons which are thought to exert their effects in the periphery.*[4]"

A few further details on the potential mechanism of action of Copaxone are summarised below. Copaxone was originally designed as a mimic of myelin basic protein (MBP), and it has been demonstrated that Copaxone has a strong affinity for major histocompatibility complex (MHC) Class II where it competes and displaces MBP.[4,5] This competition leads to down-regulation of MBP-specific T-cell activation and clonal expansion combined with induction of glatiramer acetate (GA)-reactive T-cells.[5] This mechanism has led to Copaxone being described as a 'therapeutic vaccine'.[5] Copaxone also promotes a switch in GA-reactive cells from a predominant Th1 phenotype (associated with pathological inflammation in MS) to a predominant Th2 phenotype.[5] These GA-reactive Th2 cells are able to cross the blood-brain barrier where they secrete anti-inflammatory cytokines that decrease local inflammation.[4,5]

In contrast, the beta interferons, which are derivatives of naturally occurring biological signalling molecules, act primarily through their specific receptor (interferon-α/β receptor [IFNAR]).[6] The binding of beta interferon to its receptor leads to an intracellular cascade that down-regulates the expression of MHC Class II and other co-stimulatory molecules.[4] Beta interferons also have effects on the process of T-cell migration into the CNS, with evidence of a reduction in the expression of cellular adhesion molecules, an inhibition of chemokines and matrix metalloproteinases (MMPs). These changes all act to reduce the ability of T-cells to cross the blood brain barrier and enter the CNS.[4]

The mechanisms of action of beta interferons and Copaxone can therefore be seen to be distinct from each other and this is summarised in the table below.

Table 1: Comparison of mechanisms of action for Copaxone and beta interferons [taken from Yong 2002[4]]

Mechanism	Beta Interferon	Copaxone
Antigen presentation		
Decreased expression of MHC II expression	Yes	No
Reduced level of costimulatory molecules	Yes	No
Inhibition of clonal expansion of autoreactive T-cells	Yes	Yes
Increased apoptosis of autoreactive T-cells	Yes	Not clear
Decrease of pro-inflammatory cytokines	Yes	Yes
Th1 to Th2 deviation	Not clear	Yes
Leukocyte trafficking across the BBB		
Decreased expression of adhesion molecules	Yes	No
Inhibition of chemokine expression	Yes	No
Inhibition of MMPs	Yes	No
Excludes leukocytes from entering the CNS	Yes	No
Events within the CNS		
Bystander suppression	No	Yes
Direct neuroprotection	Not clear	Possibly

This summary clearly demonstrates that Copaxone and beta interferons are unrelated compounds with distinct mechanisms of action.

The NICE Guide to the methods of technology appraisals defines a class of drugs as "*A group of drugs with the same or similar mechanisms of action. These drugs may or may not have the same basic chemical structure*."[7]

Copaxone and the beta interferons clearly do not satisfy this definition.

Paragraph 5.2.11 of the Guide to the methods of technology appraisal states:

> "*A group of related technologies might have similar but not necessarily identical effects, whether or not recognised as a 'class'. When the Institute is appraising a number of related technologies within a single appraisal, meta-analyses based on individual effects should be carried out. A class effect can be analysed as a sensitivity analysis, unless specified otherwise in the scope for the appraisal"*.

No scientific basis has been provided for concluding that Copaxone and beta interferons are even "related technologies". All they have in common is that they are both indicated for the treatment of MS and the committee does not suggest otherwise. However, even if they could be categorised as related technologies, the committee would be required to consider the individual effects of each treatment separately and may only consider a class effect (where this is valid to do so) as a sensitivity analysis.

Therefore, both from a scientific standpoint, and by NICE's own definition, there can be no rational justification of a class effect between these treatments and NICE's own procedures plainly require the committee to consider each DMT separately.

1.2 Distinctiveness of clinical characteristics

Beyond the differences in chemical structure and mechanism of action, there is further evidence of the clinical distinctiveness between Copaxone and beta interferons in a number of areas. The first of these is the adverse event profiles of Copaxone and beta interferons, which show distinct differences. In particular, Copaxone is associated with a significantly lower incidence of flu-like illness than is found with beta interferons:

- REGARD trial: 1% in Copaxone group *vs* 31% in beta interferon group ($p<0.001$)[8]
- BEYOND trial: 6% in Copaxone group *vs* 40% in beta interferon group ($p<0.0001$)[9]
- CombiRx trial: 17.0% in Copaxone group *vs* 20.4% in beta interferon group (p=NS)[10]

These trials also demonstrated that Copaxone had a significantly higher rate of transient injection site reactions (ISRs) and systemic immediate post-injection reactions (SIPRs) than beta interferons. For ISRs:

- BEYOND trial: rate was 58% in Copaxone group *vs* 48% in beta interferon group ($p<0.01$)[9]
- CombiRx trial: rate was 10.0% in Copaxone group *vs* 6.0% in beta interferon group (p=NS)[10]
- REGARD trial: overall rate was not quoted, but Copaxone had significantly higher rates of injection site itching/pruritus and inflammation ($p<0.001$)[8]

For SIPRs:

- REGARD trial: rate was 5% in Copaxone group *vs* 0% in beta interferon group ($p<0.001$)[8]
- BEYOND trial: rate was 17% in Copaxone group *vs* 5% in beta interferon group ($p<0.001$)[9]

The differences in adverse event profile are also reflected in the rate of discontinuation due to adverse events within these studies. Although none of the studies showed a significant difference in discontinuation rates, there were lower rates of discontinuations due to adverse events for Copaxone compared to beta interferons in two of the three studies:

- REGARD trial: rate was 5.0% in Copaxone group *vs* 6.0% in beta interferon group[8]
- BEYOND trial: rate was 1.8% in Copaxone group *vs* 1.5% in beta interferon group[9]
- CombiRx trial: rate was 4.2% in Copaxone group *vs* 6.8% in beta interferon group[10]

These consistent differences in the adverse event profiles reflect what is seen in clinical practice, where patients may be switched from a beta interferon to Copaxone (or *vice versa*) due to tolerability. Overall, this provides strong evidence that there is no clinical equivalence between Copaxone and the beta interferons.

Neutralising antibodies are a common issue with biological treatments; but due to its synthetic nature, they are not encountered with Copaxone. Copaxone therapy has been associated with the development of GA-specific antibodies, however, these have been found to be non-neutralising.[4,5] Neutralising antibodies were included within the Appraisal scope, but have received little attention by the AG or the committee and are not included in the latest model. Whilst Teva agrees that neutralising antibodies do not appear to cause any large differences between the clinical effects of Copaxone and beta interferons, they are another factor that demonstrates a clear clinical difference between these drugs.

It is also worthy of note that Copaxone is no longer contraindicated in pregnant women, which is important given that many MS patients are women of child-bearing age.

1.3 Evidence from clinical studies

In order for a class effect to be assumed, the NICE Guide to the methods of technology appraisal states in section 5.1.14: "*In exceptional circumstances, if the comparators form part of a class of treatments, and evidence is available to support their clinical equivalence, estimates of QALYs [quality-adjusted life-year] gained for the class as a whole can be presented*."[7] We have already explained why Copaxone and beta interferons cannot, on any view, be regarded as constituting part of "a class of treatments". The justification for clinical equivalence given by the committee in this Appraisal is that the AG "*network meta-analysis (NMA) results did not show that any particular beta interferon or glatiramer acetate was better than another*." Teva strongly believes that conclusion also fails to meet the test set out at section 5.1.14 and that this assumption cannot be scientifically justified; an absence of evidence of difference shown by the limited NMA, clearly does not provide evidence of clinical equivalence.

There are a number of weaknesses in the NMA that limit the conclusion that can be drawn from its results. The strength and reliability of a NMA relies on the quality and homogeneity of the clinical trials on which it is based, and the number of "connections" within the network.[11] In this case, there are a number of factors that weaken this NMA and therefore the conclusions that can be drawn from it, especially:

- The wide heterogeneity in the clinical trial data used in this NMA (as was noted by the AG);
- The lack of comparative trials of DMTs leading to a sparse network primarily linked through placebo;
- Disability progression was a secondary or exploratory endpoint of these clinical trials;
- The lack of statistical power for proving similarity in the underlying clinical trials; and
- The timespan covered by these clinical trials and therefore the heterogeneity in patients involved in these studies.

There is well recognised heterogeneity in the clinical trials data for MS.[12,13] This is particularly true for the data on Copaxone and beta interferons. The pivotal clinical trials for Copaxone and the beta interferons were conducted some time ago. The trials of Copaxone resulted in a Marketing Authorisation for Copaxone being granted in 2000. Since that time, there has been a number of changes to the clinical criteria used to define MS,[14,15,16] the clinical practice in the treatment of RRMS, and the other treatments available. These factors, combined with alterations in treatment paradigms and eligibility criteria in trials, have led to large changes in the patient populations within clinical trials.[17] This heterogeneity and many of its causes were highlighted by the AG in their report. The impact of the changes with time within the MS clinical trials is most clearly shown in the significant reductions in the baseline relapse rates in MS clinical trials over time ($p<0.001$), which has been documented in a number of published studies.[17,18,19,20]

The strength of a NMA is also reliant upon having a robust network with a sufficient number of active comparator trials to ensure that comparisons through placebo arms are accurate.[11] In this case, the comparisons are weakened by the relative paucity of trials comparing efficacy between DMTs. This is particularly true for the disability progression data, as illustrated by Figures 14 and 16 of the AG report, where very sparse networks were constructed that were almost entirely reliant upon comparisons through placebo. The weakness in the NMA is shown by the very large confidence intervals for the 3-month and 6-month disability progression. In all of the

included trials, disability progression was a secondary, tertiary or exploratory endpoint.[21] The weaknesses in these data mean that they cannot be considered sufficiently robust to demonstrate clinical equivalence.

Whilst the disability progression data represent the most relevant effectiveness outcome for MS and drive the cost-effectiveness modelling, the strongest evidence available is for annualised relapse rate (ARR). ARR is the most common outcome recorded and was the primary endpoint for almost all relevant MS clinical trials. In the results for ARR in the NMA conducted by the AG, Copaxone performed better than all the interferons except pegylated beta interferon, which has the least supporting data, and the highest dose of beta interferon intramuscular (44μg).[22]

The statistical power of the comparative clinical trials should also be considered as, out of the few trials comparing Copaxone to one of the beta interferons, none was designed to show equivalence. This means that the trials, even when combined, are unlikely to have sufficient statistical power to demonstrate equivalence in efficacy. This further underlines the lack of scientific evidence to demonstrate a clinical equivalence between Copaxone and the beta interferons.

1.4 Characteristics of the RSS

The RSS is not a randomised, clinical trial and, consequently, Teva fully appreciates that care must be taken when interpreting its results. However, it must also be remembered that the RSS is the only evidence that is available demonstrating efficacy in the real-world, National Health Service (NHS) population over an extended period of time. This was a principal reason why it was established.

Part of the reasoning given by the committee for the assumption of a class effect was that the RSS could be subject to selection bias meaning that "*because people in the RSS were not randomised to a specific treatment, the treatment decision, and therefore the outcomes, may have been affected by differences in the patient characteristics*."

The possibility of selection bias is a separate issue from any assumption of a class effect and provides no rational basis for pooling of data.

The RSS was not designed to provide a direct comparison between DMTs with the choice of treatment determined by the healthcare professional and patient (as would occur in real-world clinical practice). There were, therefore, likely to be differences in the populations prescribed Copaxone and the beta interferons. However, as the RSS was conducted on a single population using a single set of eligibility criteria, any heterogeneity will be much less than that seen between the clinical trials for these DMTs. The committee's rationale for clinical equivalence is somewhat contradictory in that it is based on the AG's NMA (and discounts the heterogeneity in this population) which is followed by a statement that the pooled data for the RSS should be used due to heterogeneity in this patient population (despite this being much less than in the clinical trials). These two arguments are incompatible with each other and therefore the conclusions based on any such arguments cannot be reasonable.

The RSS also provides further evidence of clinical differences between these treatments when used in UK clinical practice. The 10-year results for Copaxone were superior to the overall pooled RSS results (implied hazard ratios: [redacted] *vs* [redacted][23] for EDSS progression and [redacted] *vs* [redacted][23] for utilities), and Copaxone showed no evidence of treatment waning (unlike the pooled RSS results – see Section 2.1.2 of the original submission by Teva to this Appraisal). [redacted] The results of the RSS demonstrated a high cost-effectiveness of Copaxone which was sufficient for it to earn a price increase during the RSS, in contrast to all of the beta interferons.[24] The analysis by NICE contradicts these findings and goes against the analyses conducted by the Department of Health during the RSS.

Teva is also concerned that correspondence with NICE indicates that they are under the impression that disability progression is not a key driver of cost-effectiveness and causes little difference to ICER values. This is not true, as disability progression and health state costs are two of the factors that have the biggest influence on ICER values. This is shown by work done by the AG, in Figure 1 of Addendum 4, where a one-way sensitivity analysis was conducted that showed that disability progression ratio is the most important modelled factor in determining ICER value. The use of the pooled RSS data therefore has a considerable impact on the cost-effectiveness analyses conducted as part of this Appraisal compared to the use of Copaxone specific RSS data.

The arguments presented by the committee against the use of the Copaxone specific results from the RSS are inconsistent and questionable, as outlined above. Combined with the fact that the pooling of Copaxone and beta interferons is not scientifically justifiable, this means that the only appropriate source of data for Copaxone is its specific results from the RSS.

1.5 Comparators

Teva has always accepted best supportive care (BSC) as the main comparator for this updated Appraisal, following on from the previous Appraisal and the RSS. An important consideration, however, is that the Scope does state that '*If appropriate, the beta interferons and glatiramer acetate will be compared with each other*'. This comparison would reflect current clinical practice, where it is a choice between DMTs for these patients, not whether they would be on a DMT or BSC. The pooling of DMTs prevents this important, comparative, cost-benefit consideration that is relevant to current clinical practice. This is further emphasised by the committee's own reasoning on clinically isolated syndrome (CIS), which is based on a consideration of current practice (CIS will cease to exist as currently defined due to a change in classification, thereby leading to earlier treatment of MS).

2. Health State Costs

2.1 UK MS survey 2005/6 costs

In Addendum 4 produced by the AG before the 2nd committee meeting, an alternative set of health state costs that had not previously been considered within the Appraisal was introduced. These costs were stated to come from the UK MS Survey 2005/6 and were referenced to the single technology appraisal (STA) of natalizumab; however, their provenance was unclear based on the available documentation for this Appraisal. Health state costs are a key driver of the ICER values, as shown in the sensitivity analyses of the Teva *de novo* model; and hence the impact of this is particularly important to the results of the cost-effectiveness analysis. Due to these facts, Teva, therefore, requested clarification from NICE as to their source and validity, particularly as there appeared to be no published version of these results. The only publication referred to within the natalizumab STA (Tyas *et al*.[25]) did not include the same data as quoted by the AG. Further details from NICE have not provided clarification as they contained a number of factual errors. This lack of transparency is indicative of procedural unfairness.

The reply from NICE on 28 July 2017 stated that the costs were published in Kobelt *et al*. (2006)[26], and that further details are available in the committee papers from the daclizumab Appraisal.[27] However, the costs used in the daclizumab Appraisal are not the same as those published in Kobelt *et al*.,[26] and the committee papers from the daclizumab Appraisal state: "*the UK MS Survey is a cross-sectional postal survey funded by Biogen. It is a UK specific study, but draws heavily upon the European study of Kobelt et al*. *(2006)*."[27] It seems that, as far as Teva can determine, whilst the methodologies and analyses based on the data from this survey have been published, the specific analysis that is being used as the source of the costs for this Appraisal has not been disclosed to Teva and has never been published in a scientific journal or subject to peer-review.

Whilst it is acknowledged that these data have been used as the committee's preferred option in previous technology appraisals, it is unclear why unpublished, undisclosed data have been relied upon, when numerous other published analyses are available. These questions are heightened by the fact that the Evidence Review Group (ERG) for the natalizumab STA (where these data were first submitted) noted a number of deficiencies as follows:[28]

- Survey was funded by Biogen
- Low response rate (16%) leading to potential selection bias
- Disease state is self-assessed by respondents
- Potentially unrepresentative of MS patients in general
- Very few respondents from low (0-3) and high (9) EDSS states
- Concerns over methods of extrapolation, based on one or three month data extrapolated to a 1-year period
- Unpublished analysis
- Does not match published data using MS Survey results (Tyas *et al*. 2007)

Other data sources for health state costs were primarily excluded by the committee as they include some costs that may fall outside the remit of the NHS or personal social services (PSS). In many cases, available data

estimates of health state costs from the pure NHS/PSS perspective can be produced from the published sources, yet NICE has not attempted to do this and has relied upon an unpublished and unverifiable data source. This is procedurally unfair.

2.2 Costs inflation

Teva questions why the health state costs have been inflated to 2014/15 costs using the HCHS (Hospital and Community Health Services) index and not 2015/16 costs. The HCHS index for 2015/16 is available in the 2016 Personal Social Services Research Unit (PSSRU) publication and provides the most up-to-date estimates for costs.[29]

2.3 Uncertainty in costs

Teva believes that NICE has not fully accounted for the potential uncertainty in the health state cost figures. This is particularly important when the health state costs are a key driver of the ICER values. The NICE guide to technology appraisals states: "*There are always likely to be deficiencies in the evidence base available for health technology assessment. … Therefore, analyses should be explicit about the limitations of the evidence, and attempts to overcome these, and quantify as fully as possible how the limitations of the data are reflected in the uncertainty in the results of the analysis*." The unpublished MS Survey 2005/6 data do not include any measures of uncertainty, but the analysis by Tyas *et al*.[25] (which is based on these same data) quotes 95% confidence intervals that are around £10,000 in range for each health state just within direct medical costs. Alternative analyses, such as Karampampa *et al*.,[30] also have wide confidence intervals (£3,000 up to £7,000 depending on EDSS state). The AG undertook a probabilistic sensitivity analysis of their earlier results, but this has not been conducted on the final analysis including the committee's preferred assumptions. The AG considered the impact of variations in health state costs using the standard practice of assuming a standard error of 10% of the mean value. However, Teva suggests that an analysis that better reflects the true variation in health state costs should be undertaken, both within and also between different sources. This uncertainty in health state costs means that there could be a large deviation from the figures reported and yet this uncertainty has not been adequately addressed by NICE.

2.4 Informal care costs

The final area where Teva has concerns is regarding the exclusion of informal care costs from the analysis. Whilst Teva is aware that these fall outside of the NICE reference case, NICE guidance on appraisals states the following: "*When care by family members, friends or a partner might otherwise have been provided by the NHS or personal social services it may be appropriate to consider the cost of the time of providing this care, even when adopting a NHS or personal social services perspective. All analyses including the time spent by family members of providing care should be presented separately*." Informal care is an extremely important area in MS care, and this has been recognised by the committee's decision to include carer's disutilities within the modelling. It does not seem fair

or reasonable, therefore, that the cost benefit to the NHS of informal care is then excluded. The NICE guidance states that informal care that would otherwise be provided by NHS or PSS can be included. It is clear that, in a chronic and progressive condition such as MS, without the support of informal care the costs to NHS/PSS would be higher. Teva requests that informal care be included and accounted for within this Appraisal.

Informal care has been considered as a relevant factor by NICE in previous appraisals related to MS. The final appraisal determination (FAD) for teriflunomide stated: "*The committee understood that excluding all non-health costs was a conservative but arguably appropriate approach to adjusting the model's cost inputs to follow NICE's preferred perspective for analyses. The committee concluded, however, that the most plausible ICER was likely to lie between the ICERs estimated with and without non-health costs, given the uncertainty about how much of the non-health costs from the cited sources were within the NICE reference case*."[31] The FAD for dimethyl fumarate stated: "*The committee concluded that it preferred excluding non-medical costs, but acknowledged that the ICERs were likely to be lower for dimethyl fumarate if the personal social services costs had been included*."[32]

It should also be noted that all the available cost estimates for health states have been produced from UK patient surveys where the impact of informal care on costs will be embedded within the data. These costs are not able to reflect the cost of care for NHS/PSS that would be borne should informal care be absent. Overall, it can be concluded that it is reasonable that a consideration of informal care should be included within this Appraisal.

3. Infrastructure contributions

Teva is disappointed by the stance that NICE has taken regarding the infrastructure contributions which the RSS manufacturers committed to as part of this Scheme. These infrastructure contributions form an intrinsic part of the service delivery pathway for these DMTs and have transformed the landscape of MS care within the UK. They therefore provide a clear benefit to patients and to the NHS that is not captured within the current ICER calculations. The infrastructure contributions made under the RSS are therefore also likely to have impacted the costs as gathered from patient surveys (such as the MS Survey 2005). The potential impact that the introduction of DMTs and infrastructure contributions have had can be seen in the relative reductions that have been seen in health state costs over time.

The scope for this Appraisal states: "*If appropriate, any continuing contributions made by the companies who manufacture technologies for multiple sclerosis to the infrastructure for multiple sclerosis management, should be taken into account in determining cost effectiveness*." The infrastructure contributions were included in the RSS modelling as a discount on the annual drug acquisition cost at a rate determined by the Department of Health. This approach is the same that would be taken for a discount under a Patient Access Schemes (PAS); however, NICE has taken the decision to exclude the infrastructure contributions because "they do not match modern funding pathways." This statement is unclear and the reasoning is not understood.

Assuming the infrastructure contributions, linked to supply of DMTs, have value to patients and to the NHS, it is unfair and unreasonable that they should be disregarded by the committee.

Teva strongly requests that these contributions be taken into account for the purposes of the current Appraisal.

4. Conclusions

Teva has raised a number of concerns relating to the Appraisal process, in particular the unexpected change to considering a class effect across all treatments, which is lacking in scientific justification and inconsistent with NICE's procedures.

The changes introduced through this Appraisal (which individually are all unfair and/or not reasonable) have led to the ICER values for Copaxone changing from showing clear cost-effectiveness to borderline cost-effectiveness to Copaxone being not cost-effective (only the most recent ICER shows Copaxone as being not cost-effective). The changing ICER values for Copaxone are summarised in Table 2, with only ICER values reported by the AG included, which shows how the ICER for Copaxone has increased by a factor of 3 from the initial AG report to Addendum 4. The conclusions of the Appraisal committee can also be seen to be in direct contrast to those of its own AG, which has now published its independent report showing Copaxone to be a cost-effective treatment.[22]

Table 2: Comparison of ICER values through the appraisal process

Source	Model inputs	ICER for Copaxone *vs* BSC
AG report (as published in Health Technology Assessment[22])	Original ICER for Copaxone (using 3 month disability progression data [committee's preference])	£14,300
Addendum 2	Including carer's disutilities	£12,800
Addendum 2	Including carer's disutilities and treatment waning	£21,700
Addendum 4	Using Copaxone RSS data	[redacted]
Addendum 4	Using pooled RSS data	£27,300
Addendum 4	Using pooled RSS data and MS survey 2005 costs	£42,800

To address these issues, Teva has proposed a revised base case analysis in the following section.

5. Teva recommended base case analysis

Teva has produced an updated base case analysis based on the committee's preferred assumptions, with the following changes:

- Using the Copaxone specific effectiveness data from the RSS (alongside the Copaxone specific population data);
- Using an average of the RSS and UK MS survey 2005/6 health state costs (both inflated to 2015/16 levels; see Appendix for details of these costs and their derivation); and
- Including a consideration of the infrastructure contributions (using the methodology as previously agreed with the Department of Health for the RSS – a discount of [redacted] *per annum* on drug price).

The assumptions where Teva is in agreement with the committee are as follows:

- To apply treatment 'waning' as a 50% reduction in efficacy after year 10 (as included in the original Teva base case analysis);
- To use discontinuation rates of 5% *per* annum (as included in the original Teva base case analysis);
- To include the disutility to carers (as included in the original Teva base case analysis); and
- The updated mortality calculation technique (as included in the updated Teva base case analysis).

The committee's preferred costs from the UK MS survey 2005/6 include only direct costs and do not consider informal care; these costs are therefore likely to be an underestimate of the true costs. The health state costs from the RSS include costs other than direct cost in EDDS states 8 and 9,[27] and this might represent an overestimate of costs. Therefore, Teva has produced an alternative estimate for the health state costs, which is an average of the RSS and UK MS survey costs. This pragmatic approach should provide a better estimate of the true health state costs in MS, and mitigate some of the weaknesses in all available health state cost estimates. A similar approach has been taken by NICE in the past where there is uncertainty between two alternative estimates for a modelling input during an Appraisal; for example, in the STA for mepolizumab, the duration of exacerbations was estimated as the midpoint between the two available sources as it was accepted that one was likely to be too high and the other too low.[33] Under this updated base case, Copaxone has an ICER of £[redacted] (Table 3). In a scenario analysis, using the inflated EDSS health state costs from the RSS, Copaxone had an ICER value of £[redacted], whilst the ICER was £[redacted] using the health state costs from the UK MS survey (committee preferred).

Table 3: Comparison of ICERs under various assumptions and in the updated Teva base case analysis

Scenario	ICER for Copaxone *vs* BSC
Committee preferred assumptions – correspondence 07 July 2017	£[redacted]
Use of Copaxone specific effectiveness (& population) data from RSS	£[redacted]
Use of Copaxone specific effectiveness (& population) data from RSS and average costs of RSS and UK MS survey inflated to 2015/16	£[redacted]
Updated Teva base case (Copaxone specific effectiveness from RSS, averaged health state costs and infrastructure contribution consideration)	£[redacted]
Scenario analysis: Teva base case with RSS costs	£[redacted]
Scenario analysis: Teva base case with UK MS survey costs (committee preferred)	£[redacted]

The Teva recommended base case analysis clearly demonstrates the cost-effectiveness of Copaxone as a first-line treatment of relapsing forms of MS.

Appendix

Calculation of health state costs for Teva base case.

MS survey (from AG Addendum 4) at 2014/12 prices	MS survey inflated to 2015/16 prices	RSS cost at 1998/9 prices	RSS costs inflated to 2015/16 prices	Averaged costs (used in Teva base case)
937	949	756	1,191	**1,070**
974	987	756	1,191	**1,089**
714	724	756	1,191	**958**
3,906	3,958	1,394	2,195	**3,077**
1,892	1,917	1,444	2,275	**2,096**
3,210	3,253	5,090	8,015	**5,634**
4,285	4,342	5,678	8,941	**6,642**
11,279	11,429	17,327	27,285	**19,357**
27,472	27,838	26,903	42,366	**35,102**
21,982	22,274	34,201	53,858	**38,066**

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Title: Clinical and cost-effectiveness of beta interferon and glatiramer acetate for treating multiple sclerosis

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

All CIC (Commercial in Confidence) data has been highlighted in [redacted], all AIC (Academic in Confidence) data is [redacted]

This report should be referenced as follows:

Contributions of authors

GJMT coordinated the project, led the review of clinical effectiveness and led the drafting of the report. PA led the review of cost effectiveness, the critique of the RSS submission and the economic modelling and contributed to drafting the report. XA co-led the review of clinical effectiveness and contributed to the drafting of the report. HM and JM contributed to the economic evaluation work and contributed to drafting the report. RC contributed to the reviews of clinical and cost effectiveness through search and information specialist support and to the drafting of the report. AK and SL contributed to the review of clinical effectiveness and to the drafting of the report. CC and OC contributed as clinical experts and to the drafting of the report. JP and JR contributed to the review of clinical effectiveness and to the drafting of the report. HF contributed to drafting the report. AC supervised the project and contributed to the drafting of the report.

Please refer to the International Committee of Medical Journal Editors (ICMJE) ***Uniform Requirements for Manuscripts Submitted to Biomedical Journals see*** http://www.icmje.org/

1. Points arising in company submissions

The AG regards that the majority of the points arising in company submissions relate primarily to assumptions preferred to the committee. However, there were several observations arising, particularly in contrasting this MTA with work undertaken for TA441 (daclizumab/Zinbryta), that the AG wishes to address.

Prices converted to 2015/2016. Teva noted that prices were now out of date. We have taken this opportunity to inflate costs for EDSS health state and relapse to 2015/2016 levels from previous 2014/2015 levels. As before, we have used the committee's preferred costs by EDSS health state, which arise from the 2005 UK MS Survey. The costs we have used here, as before, arise from a 're-estimation' of UK MS Survey costs undertaken as part of TA320. That is, rather than inflate costs from 2005 levels, modellers in TA320 used unit costs released by the PSSRU to update resource use estimates from the 2005 UK MS Survey. We have inflated those costs from 2011/2012 levels to 2015/2016 levels as we regarded it to be outside the scope of our work to undertake a similar 're-estimation', and we did not have the data available to undertake this.

Continuation of treatment benefits and costs after discontinuation. Biogen noted that in the model, treatment costs and benefits appear to continue after discontinuation. The AG raised a similar concern with the DH in their original appraisal of this model. In their correspondence of 29 September 2016, they noted:

> 'Within individual cycles, as a result of the "half-cycle correction" applied in this (as in standard Markov models), the effect is that patients received a further year of treatment benefit in the year in which they discontinue treatment, but only on average half a year of costs. In following cycles, both the costs and benefits of treatment cease and patients who have discontinued treatment follow the same trajectory as patients who have never been treated. Sensitivity analysis showed that the minor inconsistency in relation to the in-cycle effects has only a very small impact on the average ICER.'

Discontinuation rates. Biogen further noted that compared with discontinuation rates used in TA441, the discontinuation rates used in this MTA appear artificially low. We note first that, as the DH communicated with us, the 5% discontinuation rate used in the RSS model (and preferred by the committee) is empirically supported by the discontinuation rates used in the RSS model. Second, the population of MS patients in TA441 is in essence different from the population of MS patients relevant to this MTA. This is reflected in the guidance for daclizumab, which includes patients whose MS has not adequately responded to prior therapy or whose MS is rapidly-evolving severe, and for whom alemtuzumab is unsuitable. Thus a lower discontinuation rate than the rate used in TA441 may

well be appropriate for a patient population using injectable interferons and glatiramer as first line treatment, given that patients using first-line DMTs will likely have MS that is less active.

Mortality multiplier used in TA441. In its original appraisal of the RSS model, the AG noted that the use of a mortality multiplier (in the original model, a standardised mortality ratio, or SMR, of 2.00) at every health state would double-count deaths, especially as EDSS 10 is a 'death state'. It also noted that an alternative option would be to use a mortality multiplier at health states prior to EDSS 10. This was implemented in TA441 using mortality multipliers from Pokorski et al (1997): namely, an SMR of 1.597 at EDSS 0-3, an SMR of 1.841 at EDSS 4-6, and an SMR of 4.436 at EDSS 7-9.

After consultation with NICE, the AG regard that this modification to the assumptions could be of interest to the committee's decision-making. Thus, analyses using the mortality multiplier are presented in this addendum using pooled estimates of effectiveness and individual DMT prices.

However, the AG also noted that the waning effect was implemented differently in Merck's presented model as compared to the model presented by the RSS and used by the AG. The AG noted that the Merck's response model (which is based on the RSS and AG models) included a change to the OFFSET function and cell reference used in the 'Waning' worksheet. In this worksheet, cell M5 [=OFFSET (M16, M3, 0)] refers to a blank cell. However in the RSS' and AG's worksheet, cell M5 [=OFFSET (M17, M3, 0)] refers to the hazard ratio ([redacted]) to be used in the first year. Using the OFFSET function allows the model to choose the appropriate hazard ratio based on the cycle length. This slight difference results in the waning effect being implemented one year later in Merck's response model. The AG analyses indicate that this leads to less than a £1000/QALY difference in the ICERs. The analyses presented implement the waning function as used in the original RSS model, rather than as modified by Merck.

2. Preliminary analysis details

We included two notable changes to the pricing structure in this analysis. First, we updated discounts as relevant. Second, we inflated UK MS Survey costs to 2015/2016 prices.

New discounts in this addendum were received for IFN β-1b 250 µg every other day (Extavia) and IFN β-1a 44/22 µg SC three times a week (Rebif). Discounts were provided in annualised form for IFN β-1a 44/22 µg SC three times a week (Rebif). Consistent with prior addenda, prices for each dose were weighted by the proportion of use in the RSS dataset.

Table 1 Discounts received by the AG as of 31 October 2017, and annualised costs

Drug	Annualised price
Glatiramer acetate 20 mg SC daily (Copaxone)	[redacted]
Glatiramer acetate 40 mg SC three times weekly (Copaxone)	[redacted]
IFN β-1b 250 µg every other day (Extavia)	[redacted]
IFN β-1a 22 µg SC three times a week (Rebif)	[redacted]
IFN β-1a 44 µg SC three times a week (Rebif)	[redacted]
IFN β-1a 44/22 µg SC three times a week (Rebif), weighted by RSS use	[redacted]

The assessment group inflated UK MS survey costs to current prices by using the hospital and community health services (HCHS) pay and price index (Curtis and Burns 2017). All results reported in this addendum are based on these inflated costs.

Table 2 UK MS survey costs inflated to 2015/16 prices

Level	2014/15 prices	2015/16 prices
EDSS 0	937	949
EDSS 1	974	987
EDSS 2	714	724
EDSS 3	3906	3958
EDSS 4	1892	1917
EDSS 5	3210	3253
EDSS 6	4285	4342
EDSS 7	11,279	11,429
EDSS 8	27,472	27,838
EDSS 9	21,982	22,274
EDSS 10	0	0

3. Analyses using DMT-specific estimates of effectiveness

The analyses for on-scheme DMTs using DMT-specific estimates of implied hazard ratio and relapse rate and individual DMT costs are presented below (see Table 3 through Table 7).

Table 3 IFN β-1a 30µg IM once weekly (Avonex), using UK MS survey management costs and the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	228,000	-	7.148	-	-
IFN β-1a 30µg IM once weekly (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 4 IFN β-1b 250 µg every other day (Betaferon), using UK MS survey management costs and the treatment waning model

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	228,000	-	7.148	-	-
IFN β-1b 250 µg every other day (Betaferon)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 5 IFN β-1b 250 µg every other day (Extavia), using UK MS survey management costs and the treatment waning model and incorporating discounts

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	228,000	-	7.148	-	-
IFN β-1b 250 µg every other day (Extavia)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 6 Glatiramer acetate 20 mg SC once daily/40 mg SC three times weekly (Copaxone), using UK MS survey management costs and the treatment waning model and incorporating discounts

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	228,000	-	7.148	-	-
Glatiramer acetate 20 mg SC once daily (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 7 IFN β-1a 44/22 µg SC three times a week (Rebif), using UK MS survey management costs and the treatment waning model and incorporating discounts

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	228,000	-	7.148	-	-
IFN β-1a 44/22 µg SC three times a week (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

4. Analyses using pooled RSS estimates of effectiveness

Next, the pairwise analyses for DMTs using pooled RSS estimates of implied hazard ratio and relapse rate against individual drug costs are presented below (see Table 8 through Table 13).

Table 8 IFN β-1a 30µg IM once weekly (Avonex), using pooled RSS estimates, the treatment waning model and UK MS survey management costs

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	228,000	-	7.148	-	-
IFN β-1a 30µg IM once weekly (Avonex)	282,100	54,100	8.047	0.899	60,200
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 9 IFN β-1b 250 µg every other day (Betaferon), using pooled RSS estimates, the treatment waning model and UK MS survey management costs

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	228,000	-	7.148	-	-
IFN β-1b 250 µg every other day (Betaferon)	271,200	43,200	8.047	0.899	48,100
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 10 IFN β-1b 250 µg every other day (Extavia), using pooled RSS estimates, the treatment waning model and UK MS survey management costs, and incorporating discounts

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	228,000	-	7.148	-	-
IFN β-1b 250 µg every other day (Extavia)	[redacted]	[redacted]	8.047	0.899	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 11 Glatiramer acetate 20 mg SC once daily/40 mg SC three times weekly (Copaxone), using pooled RSS estimates, the treatment waning model and UK MS survey management costs, and incorporating discounts

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	228,000	-	7.148	-	-
Glatiramer acetate 20 mg SC once daily (Copaxone)	[redacted]	[redacted]	8.047	0.899	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 12 IFN β-1a 44/22 µg SC three times a week (Rebif), using pooled RSS estimates, the treatment waning model and UK MS survey management costs, and incorporating discounts

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	228,000	-	7.148	-	-
IFN β-1a 44/22 µg SC three times a week (Rebif)	[redacted]	[redacted]	8.047	0.899	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 13 Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy), using pooled RSS estimates, the treatment waning model and UK MS survey management costs

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	228,000	-	7.148	-	-
Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)	282,100	54,100	8.047	0.899	60,200
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

5. Including the mortality multiplier

Finally, the pairwise analyses for DMTs using pooled RSS estimates of implied hazard ratio and relapse rate against individual drug costs are presented below (see Table 14 through Table 19). In this analysis, we also include the mortality multiplier implemented in TA441.

Table 14 IFN β-1a 30µg IM once weekly (Avonex), using pooled RSS estimates, the treatment waning model and UK MS survey management costs alongside a mortality multiplier

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	242,400	-	6.902	-	-
IFN β-1a 30µg IM once weekly (Avonex)	291,300	48,900	7.784	0.882	55,400
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 15 IFN β-1b 250 µg every other day (Betaferon), using pooled RSS estimates, the treatment waning model and UK MS survey management costs alongside a mortality multiplier

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	242,400	-	6.902	-	-
IFN β-1b 250 µg every other day (Betaferon)	280,600	38,200	7.784	0.882	43,300
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 16 IFN β-1b 250 µg every other day (Extavia), using pooled RSS estimates, the treatment waning model and UK MS survey management costs, and incorporating discounts alongside a mortality multiplier

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	242,400	-	6.902	-	-
IFN β-1b 250 µg every other day (Extavia)	[redacted]	[redacted]	7.784	0.882	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 17 Glatiramer acetate 20 mg SC once daily/40 mg SC three times weekly (Copaxone), using pooled RSS estimates, the treatment waning model and UK MS survey management costs, and incorporating discounts alongside a mortality multiplier

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	242,400	-	6.902	-	-
Glatiramer acetate 20 mg SC once daily (Copaxone)	[redacted]	[redacted]	7.784	0.882	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 18 IFN β-1a 44/22 µg SC three times a week (Rebif), using pooled RSS estimates, the treatment waning model and UK MS survey management costs, and incorporating discounts alongside a mortality multiplier

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	242,400	-	6.902	-	-
IFN β-1a 44/22 µg SC three times a week (Rebif)	[redacted]	[redacted]	7.784	0.882	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 19 Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy), using pooled RSS estimates, the treatment waning model and UK MS survey management costs alongside a mortality multiplier

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	242,400	-	6.902	-	-
Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)	291,300	48,900	7.784	0.882	55,400
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					