Public slides – part 1 (Redacted)

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

3rd Appraisal Committee meeting

Committee B, 16th November 2017

Previous Appraisal Committee meetings

November 2016 and May 2017

Companies: Bayer, Biogen, Merck Serono, Novartis, Teva

Chair: Amanda Adler

Assessment group: Warwick Evidence

NICE technical team: Thomas Palmer, Jasdeep Hayre

Key issues

- Which effectiveness estimate from the Risk Sharing Scheme should be used in the economic model?
- Which approach to modelling MS-related mortality risk does the committee prefer?
- For clinically isolated syndrome, are beta interferons and glatiramer acetate relevant in the treatment pathway?

History of this appraisal and NICE guidance

Previous Appraisal

1. **Beta interferon**
   - Rebif
   - Avonex
   - Betaferon
2. **Glatiramer acetate**

***TA32 (2002):* Not recommended**

↓

DoH Risk sharing scheme (RSS)
- Data collection on clinical outcomes

↓

RSS ended 2016

Current Appraisal

New products

1. **Beta interferon**
- Interferon 1b (Extavia)
- Pegylated interferon beta 1a (Plegridy)

2. **Glatiramer acetate**
- New formulation (Copaxone)

1st and 2nd meetings
- Long term outcome data from Risk Sharing Scheme available
- Appraisal suspended pending additional work
- No ACD issued

↓

3rd meeting TODAY
- Patient access schemes for Rebif and Extavia
- New analyses

Multiple sclerosis

Clinically isolated syndrome - CIS

- 1st clinical episode with features of MS

May not develop into clinically definite MS

Relapsing-remitting MS (RRMS)

- Clearly defined relapses
- 3 groups based on NICE guidance:
  1. RRMS
  2. Highly active
  3. Rapidly evolving
- 85-90% of people at diagnosis

Secondary progressive MS

- Some patients continue to have relapses so may continue disease modifying therapies
- ~50% within 10 years

Glatiramer acetate, IFN β-1a* and IFN β-1b indicated for CIS

All drugs indicated for RRMS

*pegIFN β-1a not indicated for CIS

Technologies – Summary

	IFN β-1a		pegIFN β-1a	IFN β-1b		Glatiramer
	Avonex	Rebif	Plegridy	Betaferon	Extavia	Copaxone
RRMS	✓	✓	✓	✓	✓	✓
CIS	✓	✓	✗	✓	✓	✓
Dose	30 mcg	44 or 22 mcg	125 mcg	250 mcg	250 mcg	20 mg or 40mg
Admin	IM	SC	SC	SC	SC	SC
Frequency	Weekly	3x/week	Every 2 weeks	Every other day	Every other day	Daily or 3x/week
List cost annual	£8,502	£7,976 or £10,572	£8502	£7264	£7,264	£6,681-£6,704
Discount?	✗	✓	✗	✗	✓	✓

RRMS: Relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; CIS: clinically isolated syndrome; IM: intramuscular; SC: subcutaneous; IFN: interferon

RRMS: Risk Sharing Scheme (RSS)

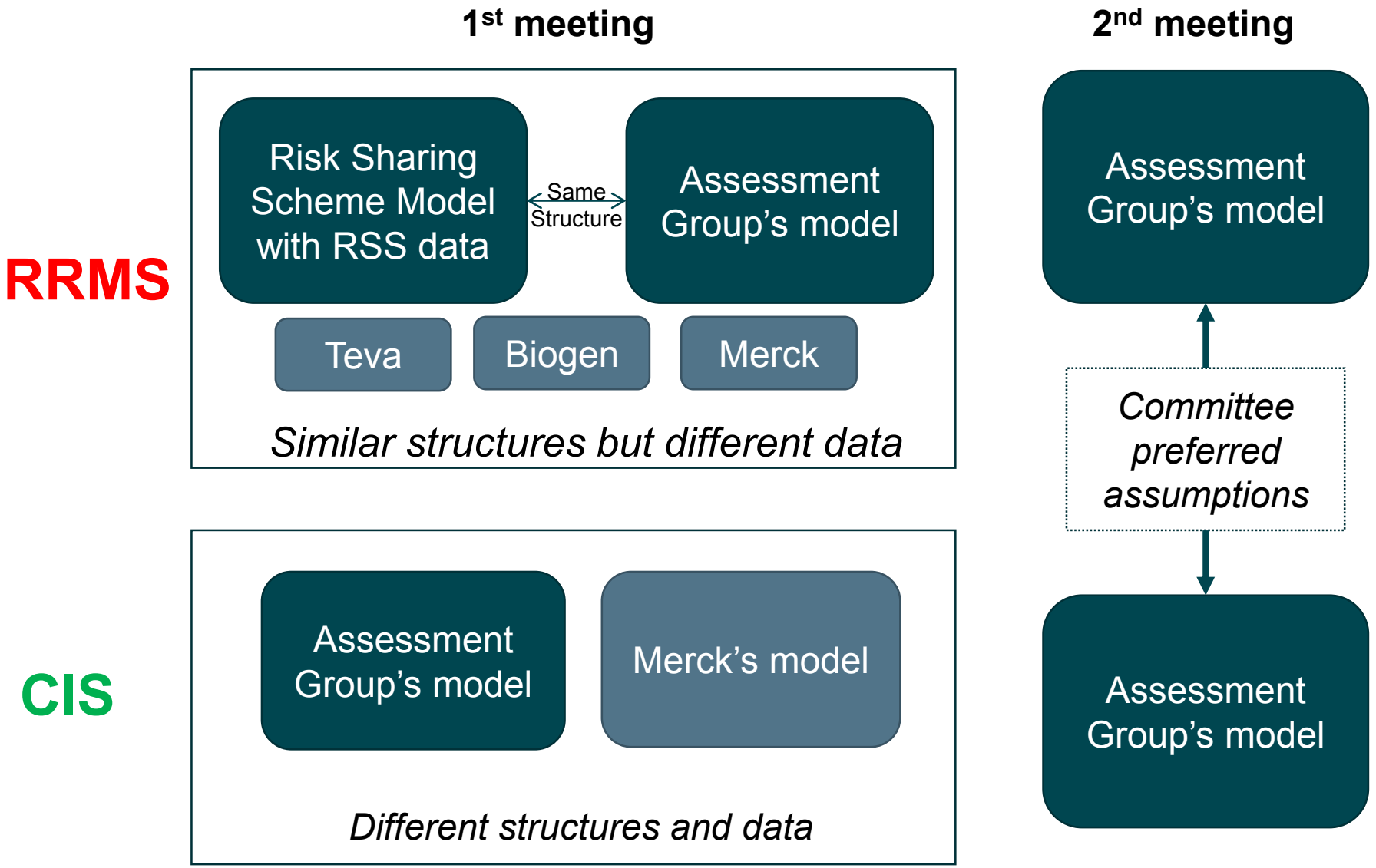
- In original appraisal (TA32), technologies not cost-effective over a 20 year time horizon
- Treatment effects based on trials with median follow-up ~2 years leading to uncertainty
- Department of Health (DoH) set up risk-sharing scheme to:
  - provide interferon β-1a (Avonex, Rebif), interferon β-1b (Betaferon) and glatiramer (Copaxone)
  - monitor whether treatments as effective as observed in trials
  - if observed benefits of treatment worse than expected from trials, then price should fall
- Risk Sharing Scheme does NOT have a 'control group' representing best supportive care
  - British Columbia Multiple Sclerosis cohort used as historical comparator
- Eligible NHS patients included anyone with relapsing remitting MS (or secondary progressive MS) who continued to relapse and who meet criteria from Association of British Neurologists
- Confidential discounts and infrastructure contributions

RRMS: Clinical effectiveness evidence

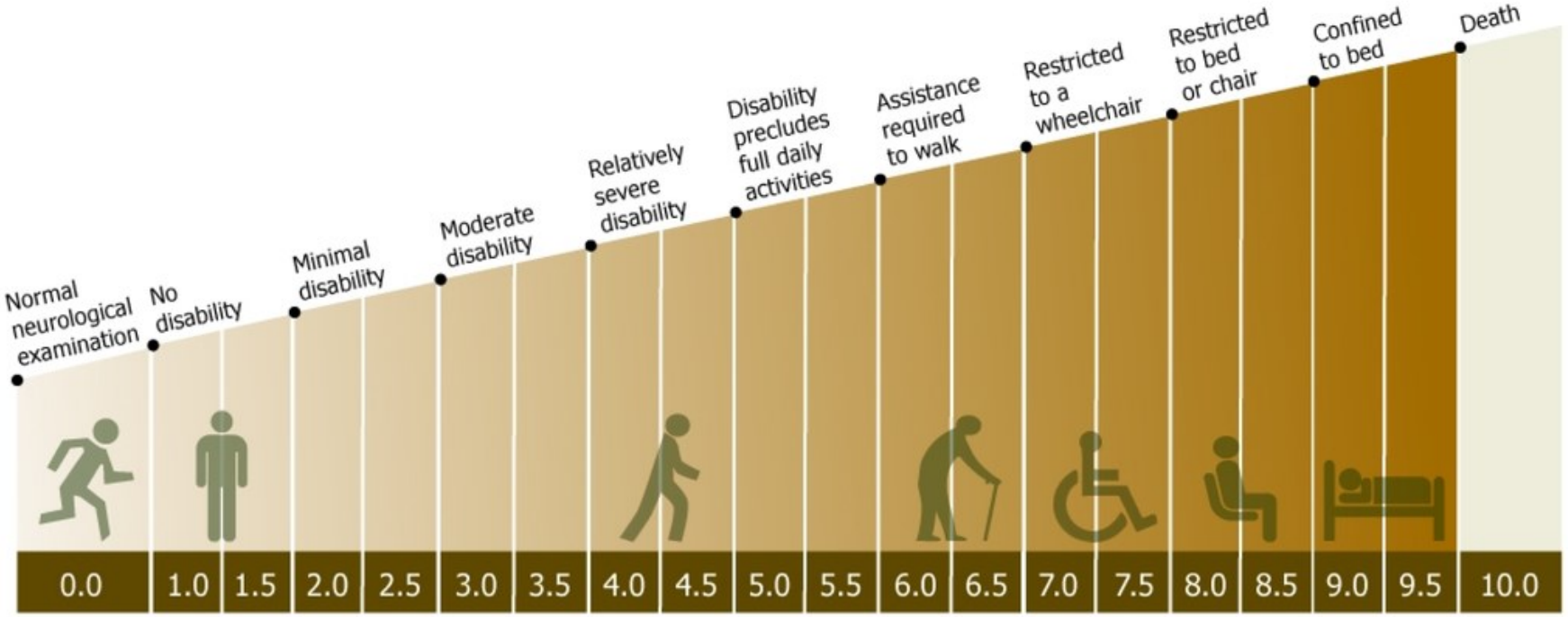
	Data from Clinical trials	Data from Risk Sharing Scheme
Source	Network meta-analyses of trials carried out by Assessment Group, Biogen, Merck and Teva	Department of Health
Key outcomes	• Confirmed disability progression • Annualised Relapse Rate (ARR)	• Summary measure of disease progression (i.e. change relative to baseline of a weighted sum of proportions of patients who progressed to each EDSS score; weighting factors = loss of utility in each EDSS)
Summary	• Point estimates broadly similar from each network meta-analysis • All drugs slowed disability progression and fewer relapses **compared with placebo** • Results comparing treatments with each other less conclusive	• All drugs slowed disability progression compared with best supportive care in historical cohort • Results for individual drugs are commercial in confidence

Issue	Committee conclusion from Nov 2016 & May 2017 meetings
Comparator	Most appropriate comparator was best supportive care
Clinical trials: RRMS	• Possible bias: difference in design, follow-up, insufficient blinding • Generalisable and relevant to consider
Clinical trials: CIS	• All technologies delayed onset of MS vs placebo • Many CIS trials before changes to definition in 2010 • Not generalisable for this appraisal
Relapse rates	• All technologies reduced number of relapses vs placebo • All technologies had similar effectiveness when compared with best supportive care
Disability progression	• All technologies delayed progression vs placebo • All technologies had similar effectiveness when compared with best supportive care
Risk sharing scheme	Preferred results from RSS as long follow-up and large number of patients (~[redacted]patients, mean follow-up: [redacted]years) • More likely to reflect reflected people treated in NHS practice
'Implied' hazard ratio	• Represents relative effectiveness in slowing disease progression as seen in the RSS, when compared with that expected from people in British Columbia MS cohort on best supportive care
Treatment Waning	Efficacy unlikely to remain constant over time

Economic models

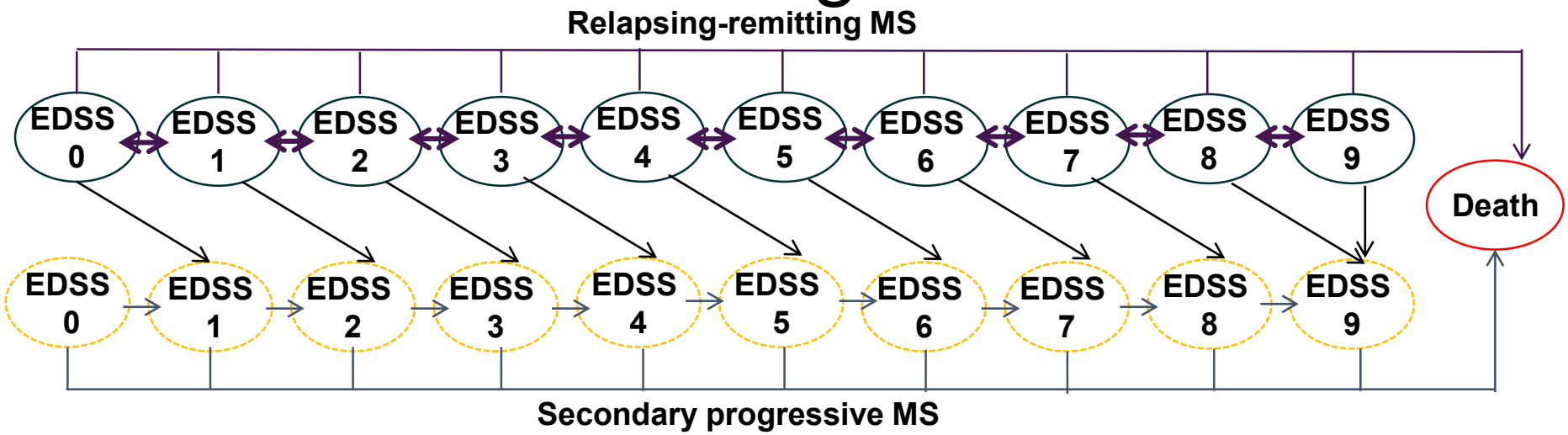


Expanded Disability Status Scale (*EDSS*)



http://www.msunites.com/understanding-the-expanded-disability-status-scale-edss-scale/

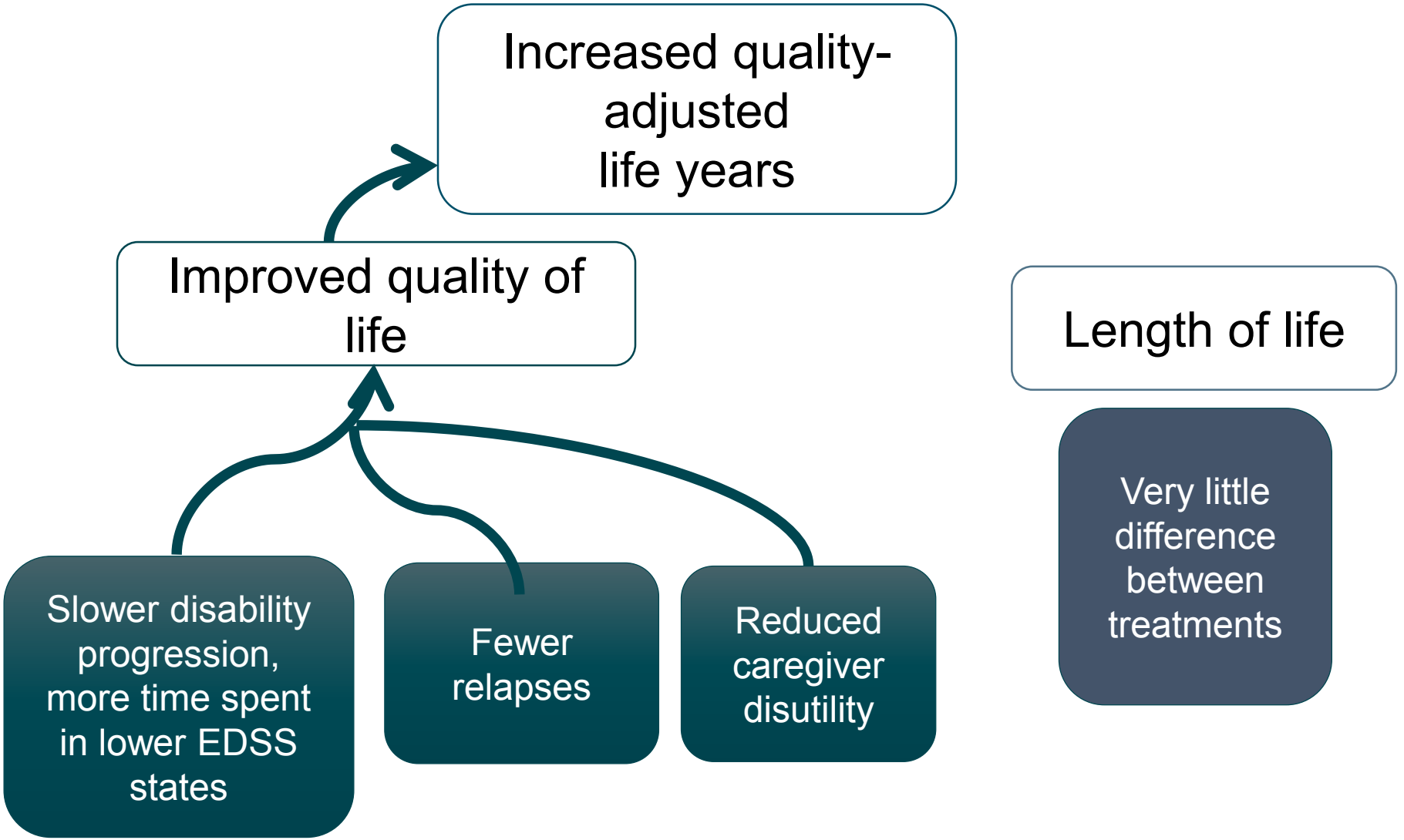
RRMS: Risk Sharing Scheme Model



Model Assumptions

- Cycled yearly
- Starting age 30 years
- Can die from MS only in EDSS 7-9
- 50-year time horizon
- Natural history of RRMS (best supportive care) based on British Columbia MS cohort (n=898)

How treatments increase QALYs in RRMS model



Risk Sharing Scheme model: effectiveness inputs

Parameter	Value	Source
Proportion of people who stop treatment each year	5%	Risk Sharing Scheme data
Annual relapse rate RR (95% CI)	0.72 (CI not reported)	MS Trust Survey 2002
'Implied' Progression HR (95% CI)	0.79 (0.77, 0.81)	Risk Sharing Scheme data

CI: confidence interval, HR: hazard ratio, RR: rate ratio

- Risk Sharing Scheme pooled results for all treatments
- **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)
- Assessment Group:
  - used RSS data in its base case
  - RSS estimate more 'robust': Network meta-analysis of trial has limited sample size & follow-up: may overestimate effects of treatment

Effectiveness of individual drugs vs pooled drugs

- RSS data (used by Assessment Group for modelling) for pooled and individual effectiveness of treatments are not directly comparable
- Pooled analysis uses all available data are used, including data after patients switch to another treatment
- Individual data excludes data after patients switch to another treatment
  - Possible source of bias, as patients who switch DMTs are likely to have experienced either worse disease progression or worse side effects
- Using pooled effectiveness estimates that are more comparable with individual effectiveness estimates (i.e. C1b below) would lower ICERs in the pooled analysis

Variant	Assumptions	Implied hazard ratio
Base-case	All data	0.7913
C1a	Excluding data after patients switch to a disease modifying therapy that wasn't in RSS	0.7793
C1b	Excluding data after patients switch to any other disease modifying therapy	0.7666

⊙ Which effectiveness estimate is appropriate for the economic model?

Results of cost effectiveness

- Not provided in public (but in part 2) because of confidential information about:
  - Effectiveness from Risk Sharing Scheme
  - Confidential discounts
- Updated from 2nd committee meeting (May 2017):
  - New patient access schemes for Extavia and Rebif
  - New assumption about mortality proposed by Merck
  - EDSS health state costs adjusted for inflation to 2015/16 levels

Issues	Committee preferred modelling assumptions (Nov 2016 and May 2017 meetings)
Natural history	Preferred British Columbia MS database
Effectiveness for RRMS	Pooled RSS effectiveness data for all treatments (including Plegridy, which was not part of the RSS)
Effectiveness for CIS	Network of trials until diagnosis of MS & data from Risk Sharing Scheme for RRMS stage
Treatment waning	Assume treatment waning (i.e. 50% reduction in effectiveness after year 10 of treatment)
Backward transitions	Assume that interferon & glatiramer acetate do not impact on backward transition (people don't improve to less severe EDSS health states)
Discontinuation from treatment	Use RSS discontinuation rates (i.e. 5% discontinue treatment every year)
Prices for drugs	Use only list prices, Commercial Medicines Unit agreements or Patient Access Scheme discounts
Utilities	Include carers' disutilities
EDSS health state costs	Preferred UK MS Survey EDSS health state costs
Analysis	Pairwise vs best supportive care

Further evidence after May 2017 committee meeting

- Some companies indicated that they were considering access agreements for their technologies, which meant that the basis for decision making was likely to change. NICE shared the main committee conclusions with the companies. In response NICE received:
- New submissions from:
  - Biogen (Avonex, Plegridy)
  - Merck (Rebif)
  - Teva (Copaxone)
- New patient access schemes from:
  - Merck (Rebif)
  - Novartis (Extavia)
- No response from Bayer (Betaferon)

Biogen
(IFN β-1a, *Avonex;* peg-IFN β-1a, *Plegridy*)

- Using RSS data inconsistent with previous appraisals → should consider individual treatment data derived from the trial-based network meta-analysis
- Using RSS for Plegridy and pooling effectiveness when individual treatment results available "inappropriate"
- Suggest that model overestimates costs, as the criterion for discontinuing treatment used incorrectly
  - Assessment Group note that this is because of the 1/2-cycle correction applied in the model
- Assessment Group overestimates treatment waning effect
  - No published evidence to support a waning effect
  - RSS already includes waning – inconsistent with previous appraisals
- Percentage of patients who stop treatment each year lower than other appraisals, with 40% of patients assumed to still be on a DMT after 10 years - does not reflect shift in treatment landscape
  - Assessment group note that the rate is based on empirical data from the RSS, and may be lower due to less active disease in RSS population

Teva (glatiramer acetate; *Copaxone*)

- No scientific justification for assumption of pooled effectiveness to include glatiramer acetate
- Uncertainty in EDSS health state costs has not been adequately addressed
  - Teva suggest using an average of the committee-preferred UK MS Survey costs and the original RSS costs (Kobelt, 2000)
- Should consider informal care costs, as Teva suggest they have been in previous appraisals (teriflunomide and dimethyl fumarate)
  - Informal care costs were not considered in either of the previous appraisals
  - In those appraisals, the committee explored analyses excluding non-medical costs because the non-medical costs **included** informal care costs
- "Unfair and unreasonable" that committee has not considered "infrastructure contributions" (contributions to the NHS)
- Should inflate EDSS health state costs to 2015/16 levels
  - Assessment group have updated the costs used in the new analyses

Merck (IFN β-1a, *Rebif*)

- Provides a new patient access scheme
- Each product should be assessed using its individual RSS results
- Merck suggest an alternative to modelling mortality risk
  - Current method: the assessment group assume that MS-related mortality is captured in transitions to EDSS state 10 and non MS-related mortality is equal to the general population
  - Merck method: Standardised mortality ratio (MS compared to general population) used for EDSS levels to capture the increased risk of mortality associated with MS
  - Reflects mortality assumptions in recent MS submissions (TA254, TA303, TA312 and TA441)

Standardised mortality ratio, SMR

- Assessment Group's original report highlighted concerns over double-counting MS-related mortality in the model
  - SMR of 2.0 was applied to general population mortality, in addition to MS-related mortality captured in transitions to EDSS state 10
  - Department of Health: SMR used to capture the increased risk of **non-MS** related mortality in MS patients
- Assessment Group changed non-MS related mortality risk to be the same as the general population, as risk of MS-related death captured in transition matrices
  - Little impact on cost-effectiveness
- An alternative approach to capturing increased risk of mortality for those with MS is using SMRs ('mortality multipliers') for EDSS states below 10
- This was implemented in previous appraisals using 'mortality multipliers' from Pokorski (1997): standardised mortality ratio of 1.597 at EDSS 0-3, 1.841 at EDSS 4-6, and 4.436 at EDSS 7-9
- Analyses using this assumption now provided by Assessment Group

Pokorski (1997) "mortality multipliers" – TA441 ERG critique

- ERG noted that data used in the model, quoted in Pokorski et al 1997, were from a secondary reference: Sadovnick et al (1992)
- Sadovnick examined mortality (115 deaths) amongst two groups of Canadian MS patients from Ontario and British Columbia (N = 2348) 1972-1985.
- Cases were classified as mild, moderate and severe MS on the basis of EDSS scores (0 to 3.5, 4 to 7, ≥ 7 respectively)
- EDSS scores were only collected at the first clinical visit, while the actual score at time of death will depend on the speed of EDSS progression in the particular population studied
- ERG expressed concerns that the study did not provide reliable estimates for making comparison with current MS population
  - Improved care and exposure to disease modifying therapies since the study, likely large differences in smoking prevalence and geographical dissimilarities

⊙ Which mortality assumption does the committee prefer?

CIS: Clinically isolated syndrome

- Clinically isolated syndrome refers to first episode of neurological symptoms
- McDonald criteria for diagnosing multiple sclerosis revised in 2010 – Can diagnose MS after a single neurological event with supporting magnetic resonance imaging (MRI)
- At **1st committee meeting:** heard that CIS patients in trials at high-risk of developing MS ("McDonald MS") would be treated as MS
- At **2nd committee meeting:** heard that relevance of CIS continues to decline, with upcoming revisions to diagnostic criteria
- Assessment Group's network meta-analysis included 5 studies, main outcome: time to conversion to clinically definite MS
- All treatments delayed the onset of MS compared with placebo
- Uncertain whether in clinical practice treatment aims to delay onset of MS, and therefore the relevance of these trials is unclear

CIS: Clinically isolated syndrome – clinician comments (1)

Due to uncertainty on clinically isolated syndrome (CIS) at the previous committee meeting, NICE contacted 4 clinical experts from recent MS-related appraisals to ask the following questions:

- **Is CIS still relevant in the clinical pathway for MS?**

"Yes…new guidelines released in 2017 may change the situation"

"Ever lesser relevance…still a group with CIS but most likely to represent the 'milder end of spectrum'"

"Yes… CIS is a holding diagnosis until we can confirm (MS)"

- **If so, how often is CIS still diagnosed?**

"About 50% of people are diagnosed as CIS and monitored for the development of MS"

"About 30-40% of patients presenting with their first attack will be CIS"

"Only about 20% of those presenting with a single event will remain having a diagnosis of CIS at 12 months…(the rest) will be diagnosed with MS at baseline following investigation or have their diagnosis changed to MS within 6-12 months due to further clinical relapse or new MRI activity"

CIS: Clinically isolated syndrome – clinician comments (2)

- **Would treatment for CIS be the same as for first-line treatment for RRMS?**

"We do not usually treat after a single episode"

"Patients remaining as CIS at 12 months are likely to represent a 'milder' group who either may never convert to MS or if they do are unlikely to have relapse frequency to qualify for a MS therapy hence this group will be far less likely to be treated"

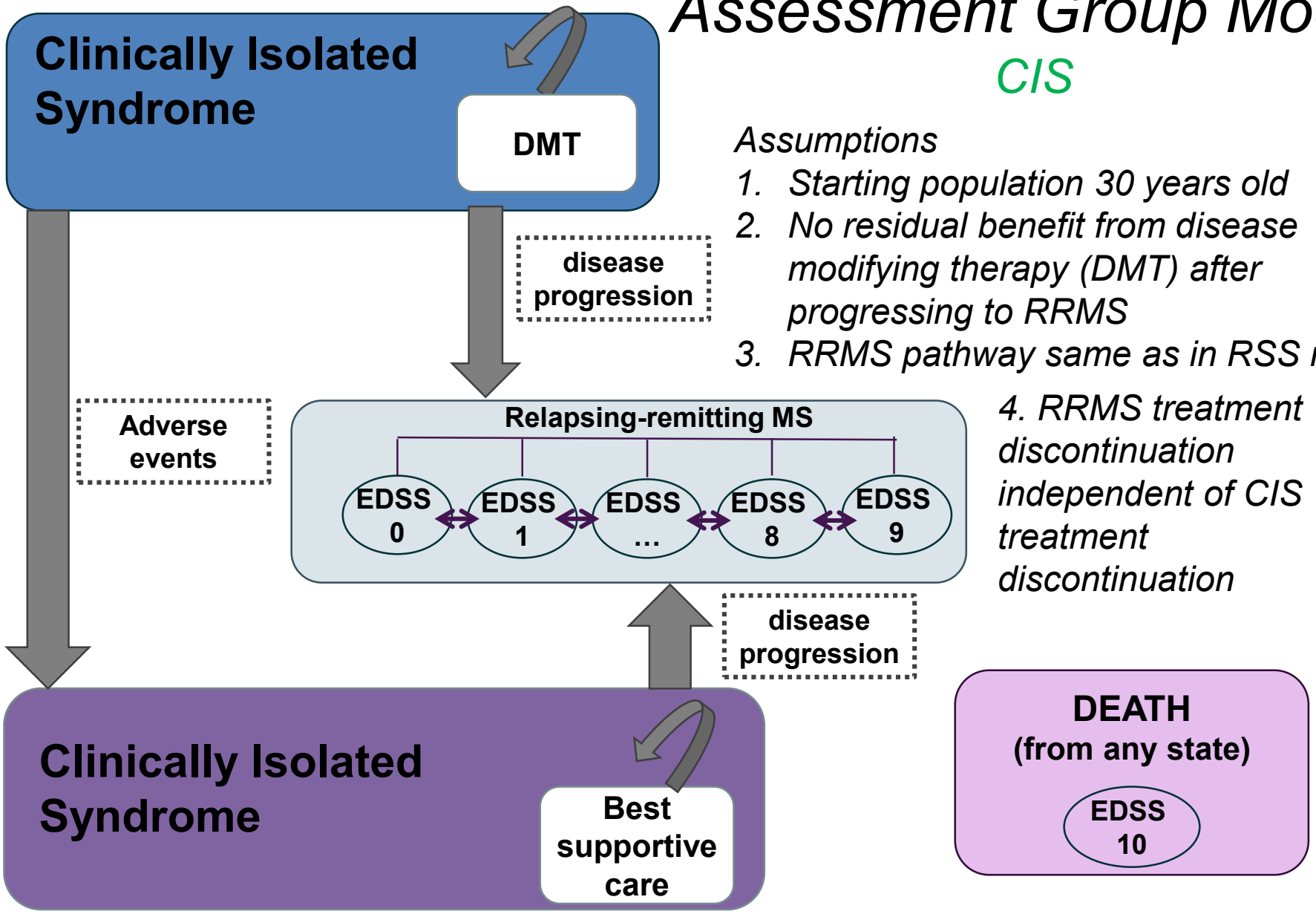
"We would not offer them treatments that are licensed for relapsing forms of MS"

"If a patient has CIS and a very active MRI we do treat as RRMS"

- Is a recommendation for treating CIS with disease modifying therapies, separately from treating RRMS, relevant for NHS clinical practice?

Assessment Group Model

CIS



Assumptions

1. *Starting population 30 years old*
2. *No residual benefit from disease modifying therapy (DMT) after progressing to RRMS*
3. *RRMS pathway same as in RSS model*

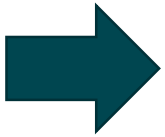
4. RRMS treatment discontinuation independent of CIS treatment discontinuation

- Does a model based on disease-modifying therapies delaying the onset of MS for people with CIS reflect clinical practice?

How treatments increase QALYs in CIS model

Clinically isolated syndrome phase:

Delayed conversion to multiple sclerosis



Increased quality-adjusted life years

After conversion to multiple sclerosis, model is the same as for RRMS:

Slower disability progression, more time spent in lower EDSS states

Fewer relapses

Reduced caregiver disutility

Key issues

- Which effectiveness estimate from the Risk Sharing Scheme should be used in the economic model?
- Which approach to modelling MS-related mortality risk does the committee prefer?
- For clinically isolated syndrome, are beta interferons and glatiramer acetate relevant in the treatment pathway?