Public slides – part 1 (redacted)

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

4th Appraisal Committee meeting

Committee B, 6th March 2018

Previous Appraisal Committee meetings

November 2016, May 2017 and November 2017

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

Chair: Amanda Adler

Assessment group: Warwick Evidence

NICE technical team: Alan Lamb, Thomas Palmer, Jasdeep Hayre

Preview of key issues

1. Pooling drugs from the RSS (assuming equal effectiveness, committee preference)
   - Pooling Plegridy, which was not in RSS, with drugs that were in the RSS
2. Biases from observational (RSS) vs. network of trials
3. Choice of treatment
4. Equality: pregnancy, unable to assemble Extavia
5. **New** prices: **new**, as-yet-approved discounts for Avonex and Plegridy; **new** glatiramer acetate (Copaxone) discount; **new** generic glatiramer acetate (Brabio)
6. Choice of data for mortality – **new** analyses by Assessment Group
7. Clinically isolated syndrome
8. Costs: Removal of treatment costs in model for people in EDSS 7–9 who would not receive treatment
9. Innovation
10. Other – e.g. infrastructural support

History of this appraisal and NICE guidance

Previous Appraisal

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

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

↓

DoH Risk sharing scheme (RSS)

- Data collection on clinical outcomes

↓

RSS ended 2016

Current Appraisal

New products

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

2. **Glatiramer acetate**
- **TODAY**: biosimilar 'Brabio'

↓

1st and 2nd meetings

- No ACD issued

↓

3rd meeting

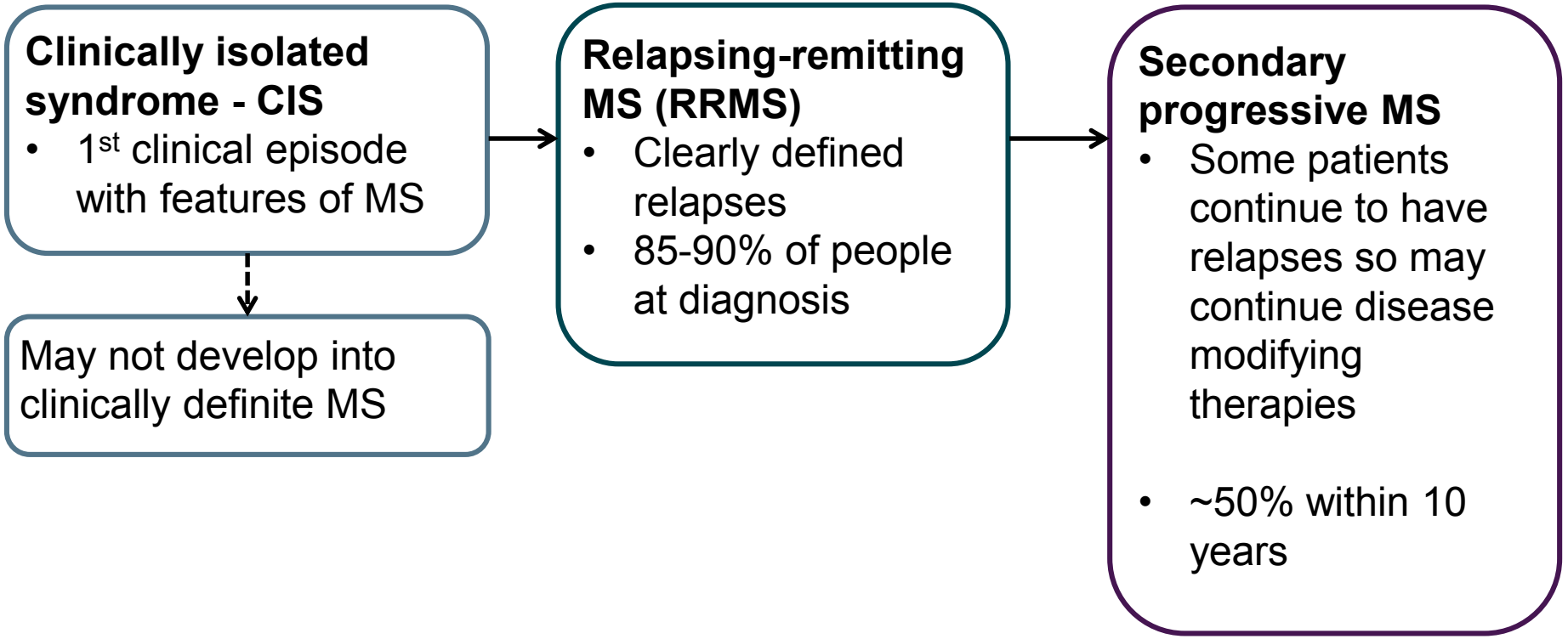
- ACD: Extavia recommended

↓

4th meeting - TODAY

- New patient access schemes for Avonex, Copaxone and Plegridy
- New analyses

Multiple sclerosis

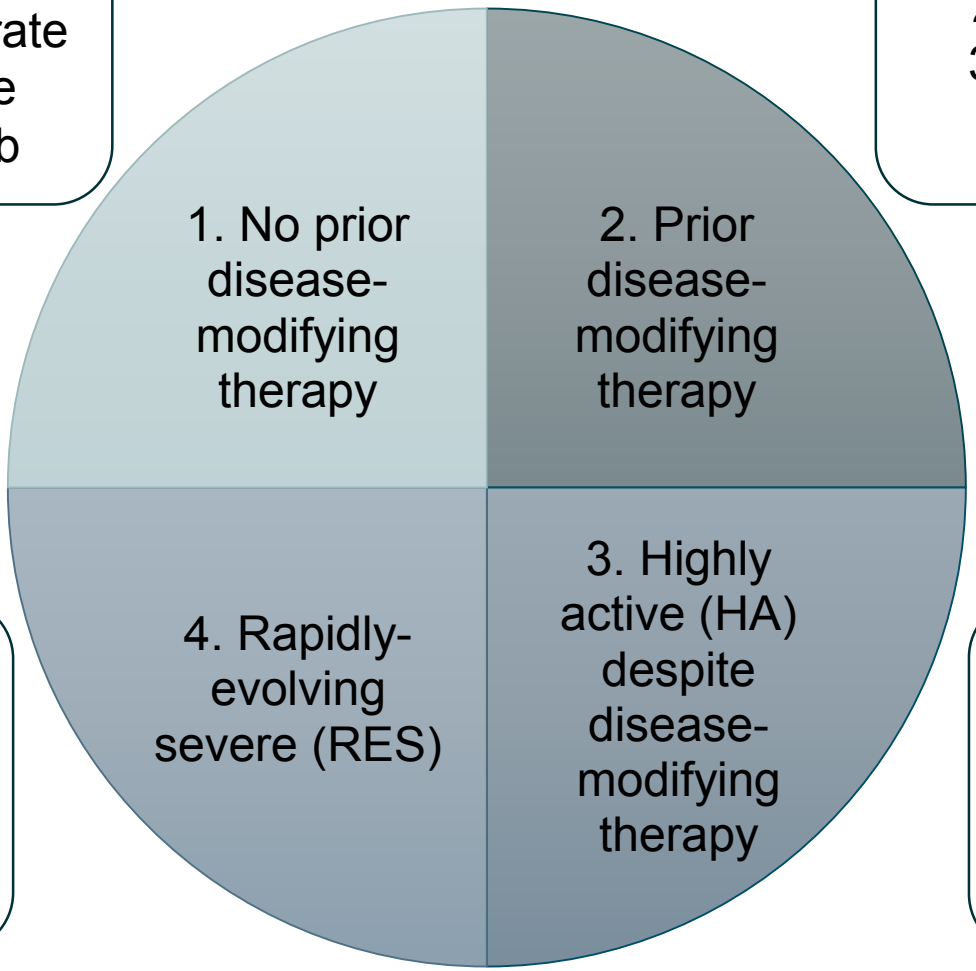


RRMS, therapies, and subgroups

1. Interferon beta
2. Glatiramer acetate
3. Dimethyl fumarate
4. Teriflunomide
5. Alemtuzumab

Prior therapy: No/Yes

1. Dimethyl fumarate
2. Teriflunomide
3. Alemtuzumab
4. Cladribine



Activity: Low /High

1. Natilizumab
2. Alemtuzumab
3. Cladribine

1. Fingolomod
2. Alemtuzumab
3. Cladribine

Technologies – Summary

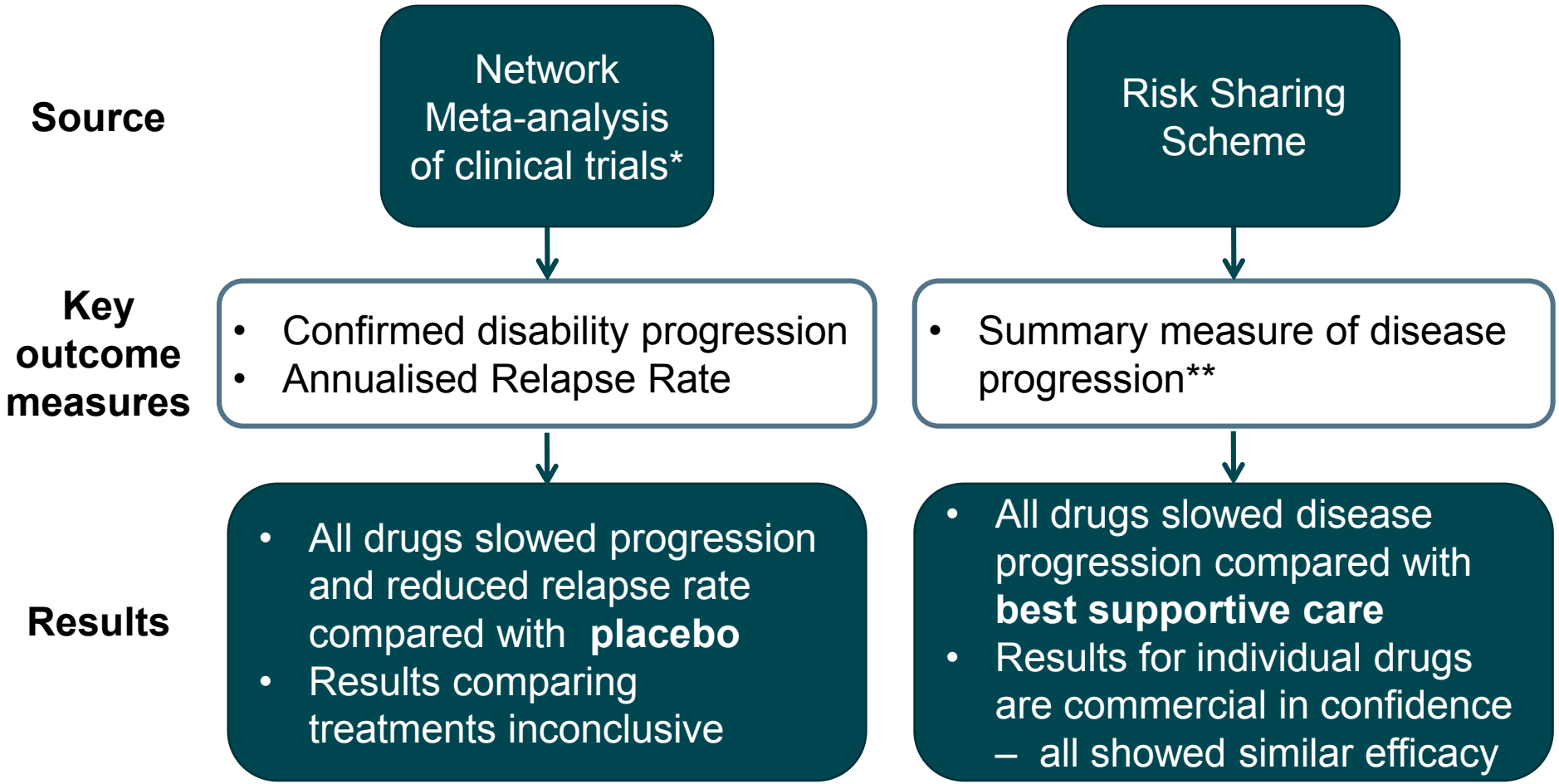
	IFN β-1a		pegIFN β-1a	IFN β-1b		Glatiramer	
	Avonex	Rebif	Plegridy	Betaferon	Extavia	Copaxone	Brabio
RRMS	✓	✓	✓	✓	✓	✓	✓
CIS	✓	✓	✗	✓	✓	✓	✓
Dose	30 mcg	44 mcg or 22 mcg	125 mcg	250 mcg	250 mcg	20 mg or 40 mg	20 mg or 40 mg
Admin	IM	SC	SC	SC	SC	SC	SC
Frequency	Weekly	3×/week	Every 2 weeks	Every other day	Every other day	Daily or 3×/week	Daily or 3×/week
List cost annual	£8,502	£7,976 or £10,572	£8502	£7264	£7,264	£6,681-£6,704	£6052
Discount?	✓	✓	✓	✗	✓	✓	✓

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

RRMS: Risk Sharing Scheme (RSS)

- In original appraisal, technologies not cost-effective over 20 year horizon
- Uncertain treatment effects as based on trials with median follow-up ~2 years
- 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
  - Used British Columbia Multiple Sclerosis cohort 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
- Companies provided confidential discounts and infrastructure contributions

RRMS: Clinical effectiveness evidence



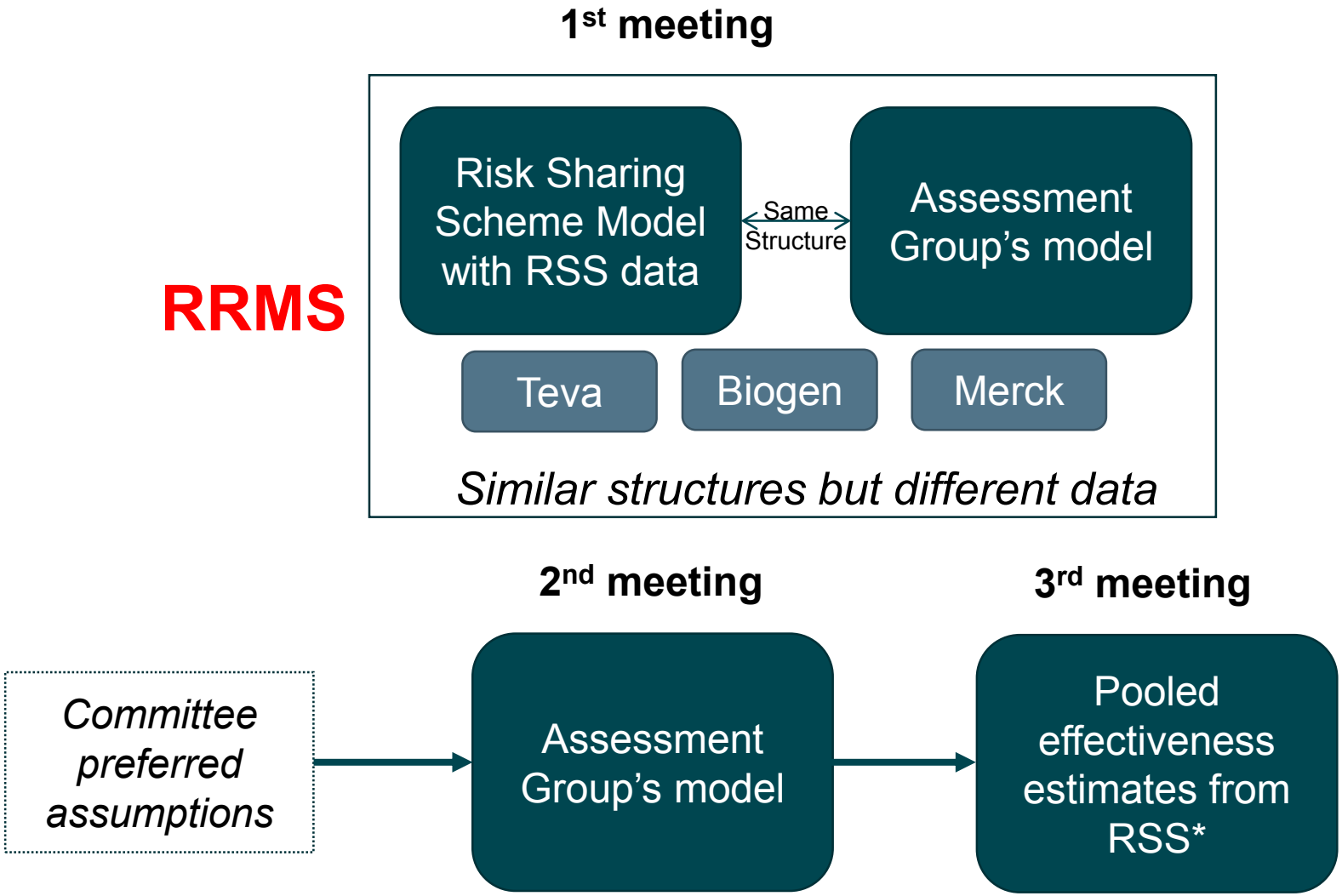
- **RSS data – pooled:** preferred by committee as provided longer follow-up and was more likely to reflect effectiveness in NHS clinical practice

*Committee preferred Assessment group network analysis over companies' analyses

**Change relative to baseline of a weighted sum of proportions of patients who progressed to each EDSS score

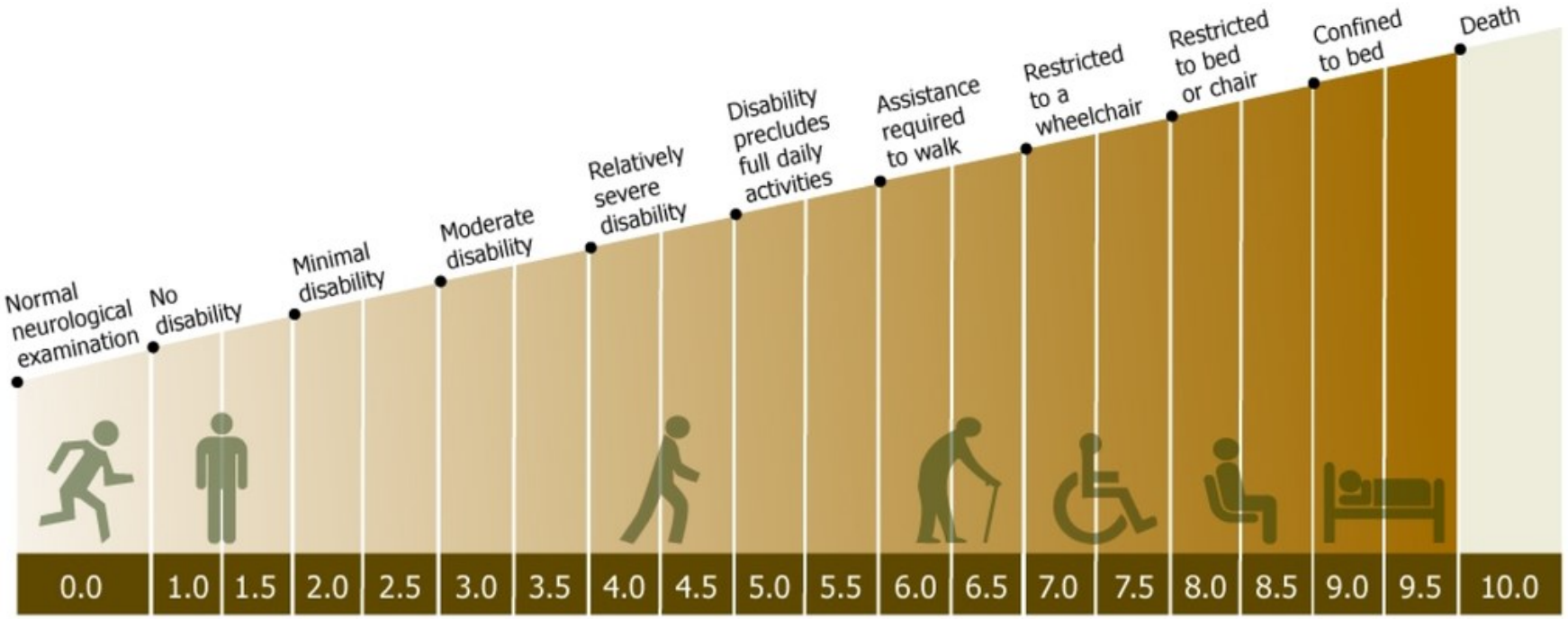
Issue	Committee conclusion previous meetings
Comparator	• Most appropriate comparator was best supportive care (ACD 3.2)
Clinical trials: RRMS	• Possible bias: difference in design, follow-up, insufficient blinding • Generalisable and relevant to consider (ACD 3.6)
Relapse rates	• All technologies reduced number of relapses vs placebo • All technologies similarly effective compared with best supportive care (ACD 3.9)
Disability progression	• All technologies delayed progression vs placebo • All technologies had similar effectiveness when compared with best supportive care (ACD 3.9)
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 people treated in NHS practice (ACD 3.10)
'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 (ACD 3.11)
Treatment Waning	• Efficacy unlikely to remain constant over time (ACD 3.15)

Economic models



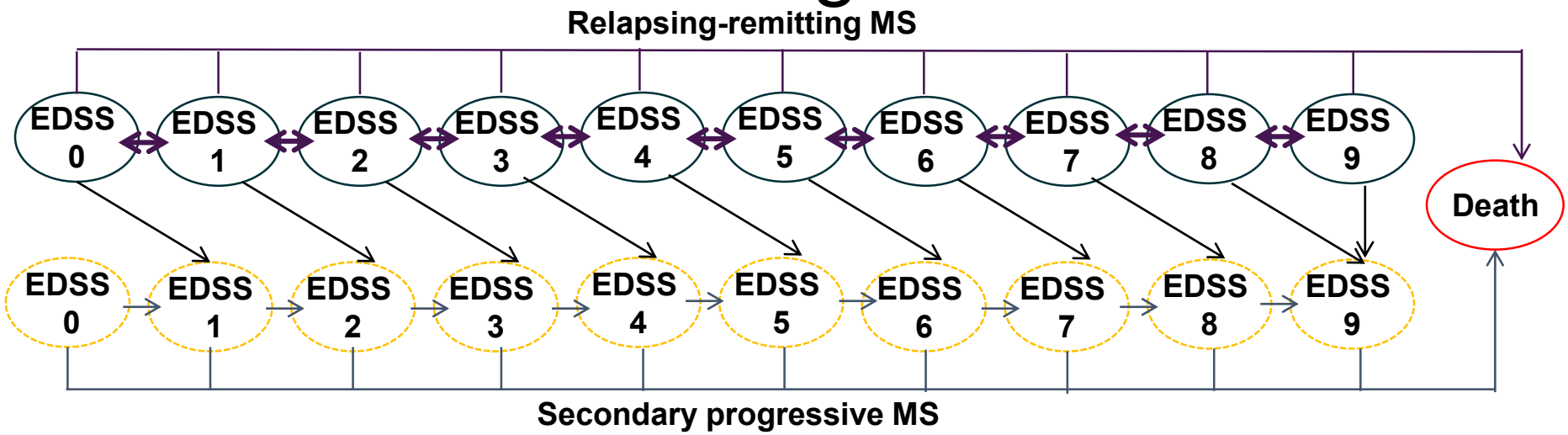
*Pooled RSS data generalised to technologies not in RSS (Extavia and Plegridy)

Expanded Disability Status Scale (*EDSS*)



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

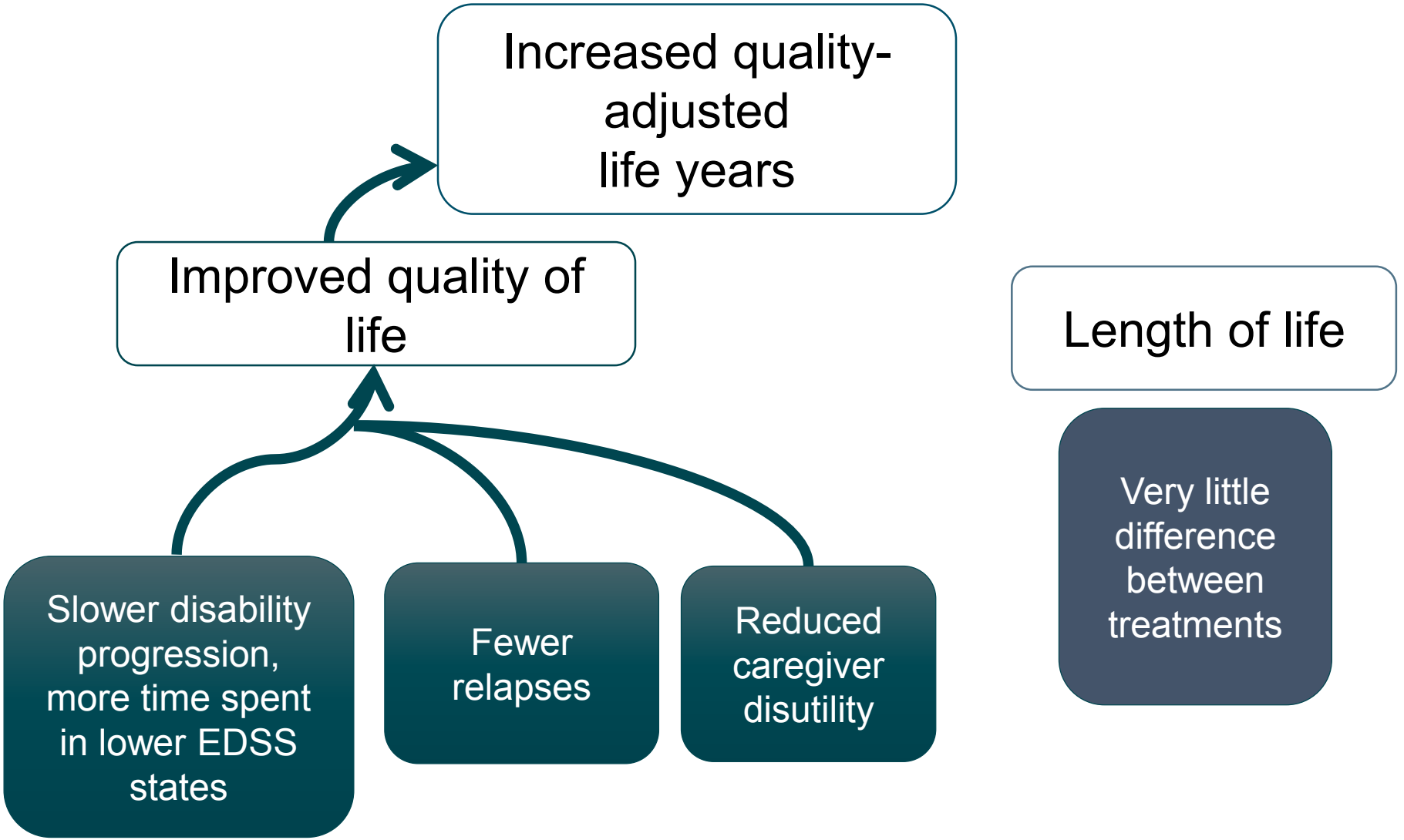
RRMS: Risk Sharing Scheme Model



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 and follow-up: may overestimate effects of treatment

Issues	Committee's preferred modelling assumptions from previous meetings
Natural history on best supportive care	British Columbia MS database (ACD 3.17)
Effectiveness of drugs	Pooled RSS effectiveness data for all treatments, including Plegridy and Extavia, which were not part of the RSS (ACD 3.13 and 3.14)
Treatment waning	50% reduction in effectiveness after year 10 of treatment (ACD 3.18)
Stopping treatment	RSS discontinuation rates of 5% of patients every year (ACD 3.20)
Prices for drugs	List prices, Commercial Medicines Unit agreements or Patient Access Scheme discounts
Utility values	Include carers' disutilities (ACD 3.21)
Informal care	Not included (ACD 3.23)
EDSS health state costs	UK MS Survey EDSS health state costs (ACD 3.22)
Analysis	Pairwise vs best supportive care
Mortality	Increased risk of mortality from non-MS-related causes not included to prevent double-counting (ACD 3.19)

Committee conclusions on cost effectiveness

- 3rd committee meeting (Nov 2017)
  - Committee concluded only Extavia was cost-effective with an ICER <£30,000 per QALY gained
  - Extavia recommended
  - No other drug recommended
  - Full details not provided in public (but in part 2) because of confidential information about:
    - Effectiveness from Risk Sharing Scheme
    - Confidential discounts

Consultation on draft guidance in Appraisal Consultation Document (ACD)

Contributing consultation comments

- Companies
  - Biogen (Avonex, Plegridy) – new as-yet-approved PAS for both
  - Merck (Rebif)
  - Teva (Copaxone) – new PAS
  - Novartis (Extavia) – recommended in ACD
- Patient groups
  - MS Trust (including survey of patients and professionals)
  - MS Society
- Professional groups
  - Association of British Neurologists (ABN)
  - UK MS Specialist Nurse Association (UKMSSNA)
  - UK Clinical Pharmacy Association (UKCPA)
- Health care professionals and the public
  - 21 patients/carers, 9 NHS professionals

PAS – patient access scheme (discount); ACD – appraisal consultation document

Topics

1. Pooling drugs from the RSS (assuming equal effectiveness, committee preference)
   - Pooling Plegridy, which was not in RSS, with drugs that were in the RSS
2. Biases from observational (RSS) vs. network of trials
3. Choice of treatment
4. Equality: pregnancy, unable to assemble Extavia
5. **New** prices: **new**, as-yet-approved discounts for Avonex and Plegridy; **new** glatiramer acetate (Copaxone) discount; **new** generic glatiramer acetate (Brabio)
6. Choice of data for mortality – **new** analyses by Assessment Group
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10. Other – e.g. infrastructural support

1. Pooling drugs together (assuming similarly effective vs. not pooling)

- **ACD**: 'committee concluded that it would use the RSS estimates representing the pooled effect in its decision-making'…network meta-analysis results did not show that Plegridy, nor any particular beta interferon or glatiramer acetate, was conclusively better than another.'
- **Company comments:**
  - 'Each product should be assessed using its individual RSS results' (*Merck*)
  - 'Teva strongly believes that the interpretation of the evidence is flawed due to the assumption of a class effect between Copaxone and the beta interferons' (*Teva*)
- **ERG:** '…compared to the real-world, longitudinal evidence provided by the risk sharing scheme, these indirect comparisons rely on short-term data from trials which are at high risk of bias… including 'matching indirect comparisons as an observational analysis …compound the two different set of biases inherent in clinical trial and observational data.'

⊙ *Has the committee seen evidence to change its decision regarding source of data?*

Effectiveness of pooled drugs vs. individual drugs

- Analyses of pooled RSS data include patients who switch treatment
  - Excluding patents who switch treatment → lower hazard ratio (treatment appears more effective)

Variant	Assumptions (based on pooled RSS data)	Implied hazard ratio
Base-case	All data including switchers	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

- Committee preferred including patients who switched treatments
- Data for individual drugs including switchers not available to Assessment Group → Teva provided individual implied HR including treatment switching
  - Analysis presented in part 2 (confidential discount)

Applying RSS pooled effectiveness to Plegridy

- Plegridy was not in RSS
- **Committee in ACD**: assumed Plegridy is as effective as other interferons as shown in Risk Sharing Scheme
- **Company (Biogen)**:
  - Committee should appraise Plegridy on the basis of its trials:
    - for effectiveness
    - for waning of effectiveness
    - for rates of stopping drug
  - Evidence for Plegridy's superiority from:
    - Existing network meta-analysis
    - non-comparative evidence for longitudinal extensions of the original ADVANCE trial
    - two matching-adjusted indirect comparisons (posters)
  - Plegridy is different: has shortest injection time, lowest administration frequency, and can be stored outside refrigerator
  - Provides new PAS (as-yet-unapproved)

Applying RSS pooled effectiveness to Plegridy
Additional evidence from Biogen

- **ACD**: '…network meta-analysis results did not show that Plegridy, nor any particular beta interferon or glatiramer acetate, was conclusively better than another.'
- **Biogen**: further evidence of indirect treatment comparisons (after matching baseline characteristics)

	Disease progression CDP @ 24 weeks	Annualised relapse rate
Plegridy vs Rebif	6.5% vs 13.2% (p=0.0007)	0.256 vs 0.335 Rate ratio: 0.76 (not significant)
Plegridy vs Avonex	5.3% vs 12% (p=0.004)	0.158 vs 0.39 Rate ratio: 0.40 (p=0.015)

Assessment group: '..the NMA included only one trial of only one year's duration for Plegridy, and that this trial that was connected to the rest of the evidence network by a placebo node alone'

⊙ *Should evidence for Plegridy, not part of the RSS, be pooled with data from RSS*?

2. Using RSS data is biased *different patients get different drugs*

- Committee aware of possibility of 'selection' bias (confounding by indication) → committee preferred pooling drugs using RSS
- Clinician and patient choice of treatment in the RSS was not random and was therefore driven by the suitability of individual treatments to individual patients (*Teva)*
- 'The pooled results will not fully reflect the efficacy of Copaxone as they include a different cohort of patients that do not receive Copaxone under NHS care' *(Teva)*
- 'Significant differences' of who gets Copaxone and who does not:
  - age in years at baseline: [redacted](with Copaxone) vs [redacted] (with beta-interferons);[redacted]
  - EDSS at baseline: [redacted]
  - years of MS at baseline: [redacted]
- *Are the differences clinically significant?*

⊙ *Has the committee seen evidence of confounding by indication?*

3. Choice of treatment

General

- 'It is in patients' interest to have the widest choice of ..therapies (*ABN*)

Mode of Delivery

- 'One of the strongest influences on why someone chooses one treatment over another is mode of delivery.' (*MS Society*)

Frequency of injection

- 20% of people in MS Trust survey identified this as a 'major' criterion (MS Trust)

Employment

- patients may prefer treatments which allow them to stay in work

Adverse effects

- 'Glatiramer acetate does not cause flu-like symptoms' (MS Trust)
- '..people have told us that they chose Copaxone …as they were informed it had fewer side effects than the beta interferons *(MS Society)*

⊙ *It is reasonable to take these factors into consideration?*

Choice: Patient/professional groups

'All MSers should have a treatment choice. It's universally accepted that no two patients experience the same symptoms, there is no reason to expect that one treatment option can fit all sizes.' Person with MS, MS Society consultation comments

'We are concerned that this recommendation lacks consideration of the following Copaxone is often favoured for ease of use, by those that don't want ongoing side effect and blood monitoring. Rebif has a very clever injection device that records times and dates of injections which helps those patients who have memory issues. Plegridy is often suited for patients not wanting frequent injections or a constant reminder of their MS.' UKMSSNA consultation comments

4. Equality issues (1) – pregnancy

- SPC: Glatiramer acetate: Preferable to avoid during pregnancy
- 'Current data on Copaxone suggests it is better from a safety [and teratogenicity] profile compared with oral DMDs is safe to use whilst trying to conceive and through pregnancy' (*UKMSSNA*)
- 'Glatiramer drug of choice in patients who are planning pregnancy' (*UKCPA*)
- "These recommendations are a harmful retrograde step …they completely remove from patients the ONLY licensed treatment with evidence of safety during pregnancy (Copaxone).' *MS specialist* Pregnancy –glatiramer acetate was the preferred treatment for women considering pregnancy and could be used in pregnant women where the benefits of continued treatment outweighed the risks. (*Teva/MS Trust*)

'I want to start a family and the only drug that has been moderately approved for pregnancy is Copaxone. To remove that drug takes away my decision between possible permanent disability or starting a family.' Patient response to MS Trust survey

4. Equality issues (2) – premixing Extavia

Extavia (recommended) requires premixing

- 'All of the drugs under evaluation, with the exception of Extavia and Betaferon, are provided as ready-to-use injection devices.' (MS Trust)
- 'Extavia is supplied as solvent and powder which must be made up each time …people with manual dexterity, visual or cognitive difficulties, all of which are common problems in MS, will find this very difficult' (MS Trust)

''In my experience Extavia is not often chosen due to the difficulties in making it up, the dexterity required and those with fatigue and busy lives aren't able to cope with this every other day.'
MS specialist response to MS Trust survey

⊙ *It is reasonable to take these factors into consideration?*

5. New prices

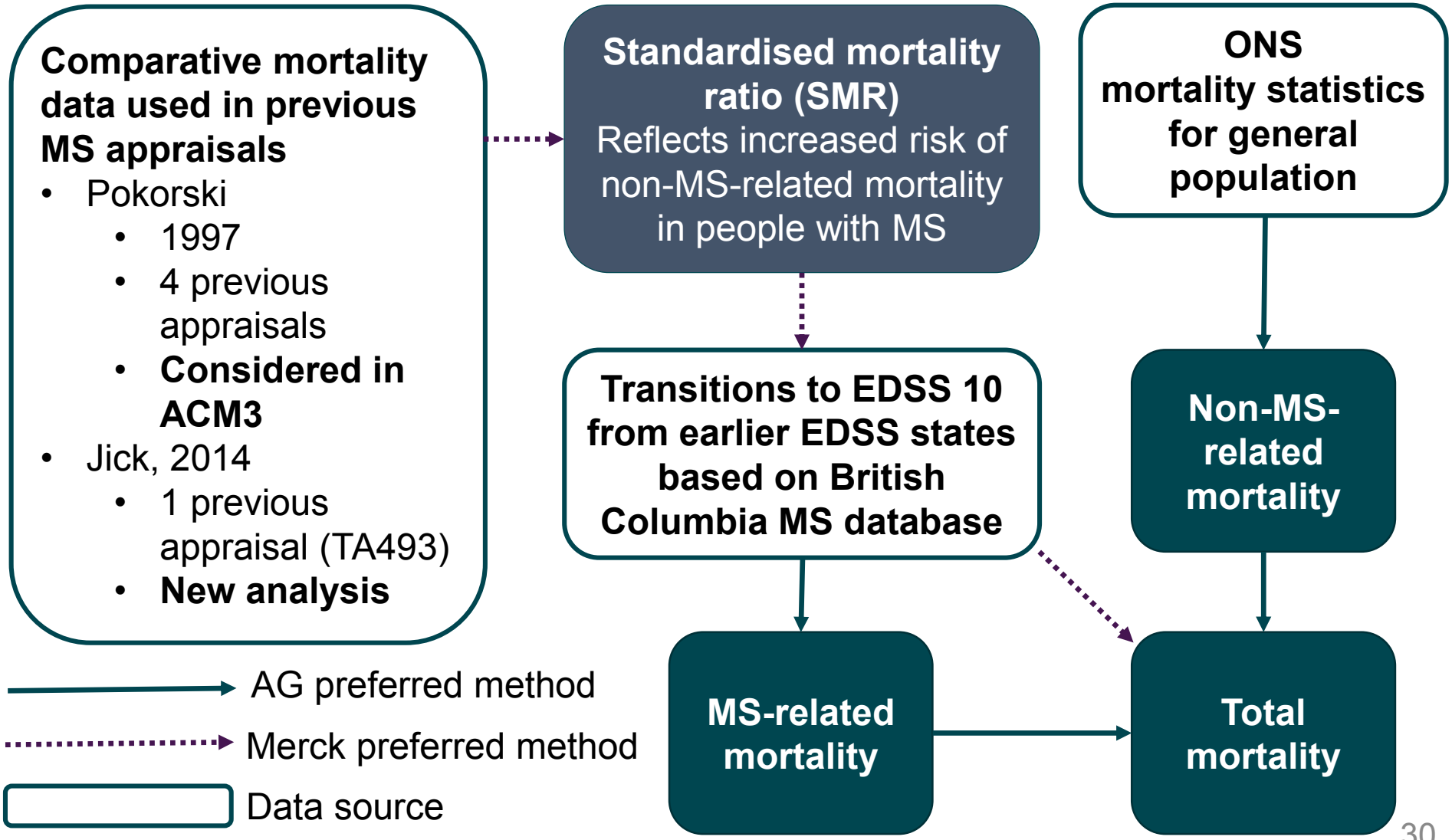
- Glatiramer acetate (Copaxone)
  - New confidential discount

- Brabio now available as (generic) “glatiramer acetate” *(ABN)*
  - *Company has provided NICE with information on proposed confidential discounts (but not yet approved)*

- *Avonex, Plegridy*
  - *Company has provided NICE with information on proposed confidential discounts (but not yet approved)*

Results of analyses using these confidential discounts provided in Part 2

6. Choice of mortality data
Current approach



Choice of mortality data – SMR

- Committee accepted approach of SMR to estimate mortality but noted Pokorski data set had limitations and overestimated mortality

Analysis	Pokorski	Jick
Year	1972–1985	1993–2006
N	2348	1822
Study location	Canada	UK
SMR	Increases with increasing EDSS state: Aligns with natural history of MS	Flat SMR of 1.50 applied: Results in clinically implausible transitions
Assessment group comments	Overestimates mortality: • improved care and exposure to DMTs • geographical dissimilarities • large difference in smoking prevalence	• Evidence is more contemporary and from UK general practice • Application of flat SMR underestimates mortality in high EDSS states → longer time spent in high cost EDSS state

⊙ Has the committee seen any new evidence favouring the use of SMRs?

7. Clinically isolated syndrome

- Clinically isolated syndrome not included in Risk Sharing Scheme
- Committee consideration in ACD:
  - Evidence from 'clinical trials using the older definition were not generalisable to current UK practice' in the NHS
  - CIS that required treating was early MS
  - Committee 'was unable to define the population or the purpose of treatment' → 'did not further consider clinically isolated syndrome'
  - Committee aware that diagnostic criteria will soon be revised, 'which may mean that clinically isolated syndrome as currently defined will cease to exist.'
- Revised McDonald criteria for the diagnosis of MS now published, the definition of CIS remains unchanged from 2010[1]
- Comments from ABN and NHS professional confirm that patients with single demyelinating event now considered to have MS

⊙ Has the committee seen evidence to change its conclusion and include CIS?

1) Thompson AJ, et al. *Lancet Neurol* 2018;17:162–73

8. Costs

- **Company**: ‘it has been noted by Teva that there appears to be a limitation within the model that leads to the inclusion of treatment costs in EDSS states 7, 8 and 9… given the changes in the treatment of multiple sclerosis that have occurred since, **it is unlikely that patients with advanced disease would continue treatment on Copaxone or beta interferons beyond EDSS 7**
- **Assessment group:** ‘one of our clinical consultants noted that even today many patients do not stop treatment at advanced EDSS stages, in part as well because the diagnosis of secondary progressive MS is often retrospective. However, **we agree with Teva that it is appropriate to model ICERs with regard to reasonable evidence based care pathway** where drugs are used within the scope of their indications.
- Analyses of the base case with treatment discontinuation at EDSS stages 7, 8 and 9 provided by Assessment Group

9. Innovation

- ‘The MS Society and MS Trust noted that the remit of the appraisal was comparison of the technologies ‘with best supportive care, rather than the newer drugs.’ The committee judged innovation in comparison with newer treatment options which ‘seems to go directly against the parameters guiding this appraisal. When compared to best supportive care, all of the treatments under appraisal should be considered innovative.’
- The MS Trust also noted that continued development since the previous appraisal in relation to reformulation (Avonex, Rebif, Copaxone), enhanced autoinjectors (Avonex, Rebif) and pegylation of beta interferon (Plegridy) could be considered as innovative by the committee.

⦿ *Has the committee heard evidence to change its conclusion on innovation?*

Other

- Model doesn't capture difference in utility from industry support programmes ('infrastructural' support)
  - Merck, for example, offer an extensive personalised patient support programme (PSP) with Rebif, which utilises one-to-one nursing support and training sessions, a dedicated nurse helpline and offer additional education and information on Rebif.' (*Merck*)
- Infrastructure costs were previously considered by the committee but were not considered appropriate to include

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