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]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Biogen
   - Merck Serono
   - Novartis
   - Teva Pharmaceuticals
   - Multiple Sclerosis Society
   - Multiple Sclerosis Trust
   - Association of British Neurologists
   - United Kingdom Clinical Pharmacy Association
   - United Kingdom Multiple Sclerosis Specialist Nurse Association

   Sanofi Genzyme and the Department of Health and Social Care stated that they had no comments

3. **There were no comments received from patient or clinical experts.**

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Assessment Group addendum**

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

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

Multiple Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	Biogen Idec Ltd	Biogen is disappointed by the current decision to only recommend Extavia (interferon beta 1b) as an option for treating multiple sclerosis. Copaxone, Avonex and Rebif, Betaferon and Plegridy have not been recommended based on cost-effectiveness grounds based on pooling of the risk sharing scheme data and lack of consideration for patient and clinician preferences e.g. injection frequencies, routes of administration and incidences of neutralising antibodies. As stated throughout the process we disagree with the committee's preferred methodology and assumptions. In our view, the approach is unjustified given the evidence available, in particular in the handling of Plegridy. In the first assessment group report, it was concluded that Plegridy, at list price, was the most cost-effective treatment, dominating (i.e. more effective and less costly) or extendedly dominating all other treatments when treatment specific efficacy and safety were considered. This current recommendation is a stark contrast to the original report where Plegridy is not considered cost-effective. Plegridy is classified as a new chemical entity and was not included in the risk sharing scheme and unlike Extavia does not have an equivalent product (e.g. betaferon) that did participate in the scheme. It is therefore not plausible to evaluate Plegridy through the pooled data derived from this source. There is a large body of evidence to support the high clinical efficacy of Plegridy in patients with relapsing remitting multiple sclerosis. Moreover, the design of the pivotal clinical study ADVANCE (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. ADVANCE is a modern era study in a patient population most likely to receive beta-interferons and glatiramer acetate in UK clinical practice. A total of 2,000 patient-years of experience were accumulated in the study which demonstrated:	Thank you for your comments. The committee's considerations about patient and clinical preferences are outlined in the FAD sections 3.3 and 3.11. Plegridy is no longer being considered as part of this review (ID809) and will be considered in a separate Single Technology Appraisal.

			• Plegridy significantly reduced the frequency and risk of MS relapses over 1 year, compared with placebo
			  o Plegridy significantly reduced annualised relapse rate by 35.6% at 1 year, compared with placebo (0.256 vs 0.397, p=0.0007).
			  o Proportion of patients relapsed at 1 year was significantly reduced by Plegridy, by 39% compared with placebo (90 vs 142, p=0.0003).
			• Plegridy significantly reduced the risk of sustained disability progression, compared with placebo
			  o Plegridy significantly reduced the proportion of patients with disability progression sustained for 3 months by 38% over 1 year, compared with placebo (0.058 vs 0.105, p=0.0383).
			  o Plegridy significantly reduced the proportion of patients with disability progression sustained for 6 months by 54% over 1 year in a post-hoc analysis, compared with placebo (0.040 vs 0.084, p=0.0069).
			• Plegridy significantly reduced inflammatory disease activity as measured by MRI at year 1, compared with placebo
			  o 67% fewer new or newly enlarging T2 lesions (3.7 vs 10.9, p<0.0001).
			  o 86% fewer gadolinium enhancing (Gd+) lesions (0.2 vs 1.4, p<0.0001).
			  o 53% fewer T1 lesions (1.8 vs 3.9, p<0.0001).
			
			At the conclusion of the 2-year ADVANCE study, patients were eligible to enter an extension study (ATTAIN). As per the Summary of Product Characteristics (SmPC), 658 patients have completed 4 years in this study programme. Patients receiving continuous Plegridy since Year 1 of the ADVANCE trial (N=376) continued to show low adjusted ARR into Year 6 (0.055–0.203) and low mean number of MRI lesions (new T1 [0.7–0.8], new/newly enlarging T2 [1.9–2.0], Gd+ [0.2–0.3]) up to Year 4. Sustained disability progression confirmed over 6 months also remained low in patients receiving continuous Plegridy, with only 14% of patients experiencing progression at Year 6. This is often a key indicator of efficacy for clinicians and further supports the value that Plegridy offers to patients with MS.
			The above long-term data has been presented in our original manufacturer submission and in responses to prior consultation but has not been considered by the committee due to lack of apparent statistically significant differences observed in the meta-analysis which is driven by the underlying heterogeneous clinical trials. Therefore, under the current recommendation, an unpublished observational study, which Plegridy did not participate in has been used instead of using Plegridy's own pivotal studies. We disagree with this approach and believe decision making for Plegridy should be based on its own data. Comparing or combining robust randomised controlled trial data with the risk sharing scheme data may be methodologically difficult, however this does not justify the current approach.
			We are happy to work with NICE to determine a more suitable methodology where both sets of data can be incorporated and are exploring this independently.	

			It should be acknowledged there is also an ongoing technology appraisal for relapsing remitting multiple sclerosis (e.g. Ocrevus [ocrelizumab]) outside of the current MTA for which NICE should be seeking to implement consistent methodology (i.e. use of risk sharing scheme data combined with randomised controlled trials). **Both Plegridy and Ocrevus are new chemical entities and should be treated similarly.**	
2	Company	Biogen Idec Ltd	Use of the pooled risk sharing scheme effectiveness data in comparison to individual treatment data underpins the perceived lack of cost-effectiveness for the beta interferons and Copaxone not being recommended as part of this ACD. The risk sharing scheme data lacks transparency, is currently unpublished and observational in nature, falling lower in hierarchies of evidence than gold standard randomised controlled trials and meta-analysis. There are several recommendations for assuming class effect within the literature, most with stricter criteria than NICE, however we believe the more lenient NICE criteria used in this MTA were not even met in the risk sharing scheme which was used to inform the economic model of this appraisal. Assumptions of class effect should not be based on efficacy alone, but should also be based on safety. Head to head evidence should be provided to support any assumptions. The supporting evidence for safety was lacking and limited to 'discontinuations due to adverse events' alone. Severe adverse events, adverse events quality of life, were not considered and therefore an assumption of class effect cannot be considered robust. There was direct evidence presented in the assessment report that illustrated evidence of significant differences in treatment effects for different products under consideration (and different regimens of drugs) as presented in prior consultation responses, this is at direct odds with an assumption of a class effect. As previously mentioned, the risk sharing scheme was never designed to assess a class effect but to only ascertain cost-effectiveness of an agent against itself. The risk sharing scheme was always going to show non-inferiority (no statistical significance) when comparing products due to heterogeneity; as confirmed with the wide confidence intervals. Biogen appreciate the complexity and understand the rational for using the risk sharing scheme data as it would be relevant to the UK population, however its use should be only restricted to the agents included within the RSS, namely Avonex, Rebif, Copaxone, Betaferon. Using this data to assess the cost-effectiveness of Plegridy is adding further uncertainly to a model that already possess high levels of uncertainty. In contrast, data from matched, adjusted indirect comparison studies have shown Plegridy to demonstrate better clinical outcomes when compared to interferon beta-1a (Rebif and Avonex): ▪ Coyle PK et al. presented results (poster) at the America Academy of Neurology 2017 of a matching-adjusted indirect comparison utilising four Phase III trials of Rebif	Thank you for your comments. The committee was aware that evidence on efficacy, adverse events and quality of life had been considered in the assessment group's network meta-analysis and systematic literature review. Please see section 3.10 of the final appraisal determination. Plegridy is no longer being considered as part of this review (ID809) and will be considered in a separate Single Technology Appraisal.

			versus Plegridy. The results at 2 years showed that the proportion of patients with disability progression confirmed at 6 months was statistically significantly lower in the Plegridy group compared to Rebif (6.5% versus 13.2%; p = 0.0007). There was also a lower annualised relapse rate (RR = 0.76, ns). ▪ Scott T et al. presented the results (poster) at the American Academy of Neurology 2017 of a matching-adjusted indirect comparison of clinical effectiveness comparing Plegridy versus Avonex. The results at 2 years showed a statistically significant lower proportion of patients with confirmed disability progression and annualised relapse rates with Plegridy. **The above two studies suggest that Plegridy is different to the other beta-interferons when trial population baseline characteristics are matched, and should be treated on its own as opposed to integration with the RSS data and class effect.**	
3	Company	Biogen Idec Ltd	Beta-interferons and glatiramer acetate are grouped together as a single treatment class within this appraisal and therefore may incorrectly be considered interchangeable with no differences in their clinical profile. However, there are important differences between these treatments which may provide patient-level and economic benefits. This is particularly relevant when the heterogeneity of both MS and patient preferences are considered, as these differences can make certain treatments more appropriate for individual patients and therefore impact adherence (as also demonstrated by the differing baseline characteristics and the propensity to be treated with a particular treatment within the risk sharing scheme). In this appraisal, little consideration has been given to differentiating factors beyond efficacy between the beta-interferons and glatiramer acetate due to the current pooling assumptions. Apart from the efficacy advantages already highlighted in this document, Plegridy has additional differences that are of value to patients, for example: • Plegridy is available in a single use, disposable auto-injector which requires no reconstitution, assembly, or disassembly, has the shortest injection time of any IFNβ device (5 seconds vs 10 seconds), and has a needle cover lock to assist in avoiding needlestick injury. • No cold chain storage is required for up to 30 days in comparison to other beta-interferons up to 25 degrees Celsius. This allows flexibility for patients when travelling, not having the hassle of needing to keep their therapy in cold chain; and if travelling for less than 2 weeks, would not require travel with their drug. • Plegridy has the lowest administration frequency per year (26 injections/year), followed by Avonex (52), Rebif (156), Copaxone 40 mg (146), Betaferon/Extavia (183) and Copaxone 20mg (365). Lower administration frequencies are linked to improved adherence, which has been shown to result in improved clinical outcomes	Thank you for your comments. The committee considered the company's comments. The committee noted that the benefits of ease of preparation and administration conferred by auto injection devices compared to premixing of powder and solvent required for Betaferon and Extavia were not captured in the cost-effectiveness analysis. Please see sections 3.29 and 3.30 of the final appraisal determination. Plegridy is no longer being considered as part of this review (ID809) and will be considered in a separate Single Technology Appraisal.

			and lower disease management costs (Devonshire et al, 2011; Menzin et al 2013; Ivanova et al, 2012; Steinberg et al, 2010; Tan et al, 2011; Treadaway et al 2009). **If the above factors were not considered important by clinicians and patients alike, we would expect to see greater parity in uptake between the beta-interferons and glatiramer acetate in clinical practice, which is not the case**.	
4	Company	Biogen Idec Ltd	Beta-interferons and glatiramer acetate have been a mainstay of treatment for relapsing remitting multiple sclerosis since their introduction; however, patients may develop neutralising antibodies (NAbs) against beta-interferons which can reduce the efficacy of treatment and have been postulated in prior NICE appraisals to be directly linked to treatment waning. The reported incidence of NAbs in patients with MS varies between <1% and 42%, depending on the beta-interferons tested. Glatiramer acetate is not associated with NAbs. Data from a study by Grossberg et al (2011) show that Avonex has the lowest incidence of NAbs (5-8%) of any beta-interferon; while Plegridy was not available at the time of this study, a study by White et al and the summary of product characteristics (SPC) indicates that NAbs are even less likely with this product (data from patients treated up to 2 years with Plegridy suggests that less than 1% developed persistent NAbs to the interferon beta-1a portion of peginterferon beta-1a). Current waning assumptions applied in the economic model are arbitrary (50%) and in this particular instance where the year 10 implied hazard ratio is used, is overestimating waning when compared to assumptions used in more recent technology appraisal e.g. TA320 (alemtuzumab) and TA 441 (daclizumab) where step changes are applied to 2-3-year data. **We request that the assessment group run further analyses on the risk sharing scheme data to identify the degree of waning specific to each treatment given these reported incidences.**	Thank you for your comments. The committee considered the company's comments. Treatment waning was accounted for within the Risk Sharing Scheme model during the 10 years of follow up. The assumption in the extrapolated part of the model of a 50% reduction in effect from 10 years onwards is consistent with the waning assumptions applied in previous appraisals. Please see section 3.19 of the final appraisal determination. Plegridy is no longer being considered as part of this review (ID809) and will be considered in a separate Single Technology Appraisal.
5	Company	Biogen Idec Ltd	We believe the parity assumption of a 5% annual discontinuation rate (seemingly derived from empirical evidence from the risk sharing scheme) is not applicable to Plegridy which was not included in the scheme and is in contrast to both ADVANCE and ATTAIN. **We request the assessment group and committee provide justification for this assumption given the contrasting evidence available from randomised controlled trials for Plegridy.**	Thank you for your comments. The committee considered the company's comments. The committee understood that higher discontinuation rates implausibly improved the cost-effectiveness of treatments. Please see

			We also request the assessment group considered year by year data from the scheme to populate the economic model which has the flexibility to consider year 1, year 2 and year 3+ data.	section 3.23 of the final appraisal determination. Plegridy is no longer being considered as part of this review (ID809) and will be considered in a separate Single Technology Appraisal.
6	Company	Biogen Idec Ltd	Clarification on page 9, section 3.1. It is stated that "The scheme was set up so that if the drugs were less effective than anticipated, the price would fall", we suggest for transparency, text is also included also stating the counter i.e. "if drugs were more effective than anticipated, the price would increase". The latter occurred for one of the included products during the scheme. Up to year 10 none of the included products performed worse than anticipated and there were no price decreases as a result.	Thank you for your comments. This has been amended, please see section 3.1 of the final appraisal determination.
7	Company	Biogen Idec Ltd	Factual inaccuracy: page 6 Plegridy (interferon beta 1b) should be Plegridy (pegylated interferon beta 1a); similarly, Extavia (pegylated interferon beta 1a) should be Extavia (interferon beta 1b)	Thank you for your comments. This has been amended, please see page 5 of the final appraisal determination.
8	Company	Biogen Idec Ltd	In accompaniment to the above proforma response, we have also submitted a supplementary appendix containing cost-effectiveness results using recently submitted confidential PAS proposals for both Avonex and Plegridy.	Thank you for your comments. This was considered by the committee.
9	Company	Merck Serono	We are surprised and disappointed with the NICE Committee's preliminary decision in the MTA of the interferons and GA for MS, following protracted deliberations during 2017. In Merck's view, the outcome is incompatible with the case that has been presented for Rebif (both in this MTA and indeed in the Risk Sharing Scheme itself) and, even more importantly, the resulting recommendation is unsuitable for MS patients, their physicians and indeed for the NHS.	Thank you for your comments. Rebif is now recommended as an option for people with relapsing-remitting multiple sclerosis. Please see section 1.1 of the final appraisal determination.
10	Company	Merck Serono	1. Rebif is a well established, well tolerated, efficacious and cost-effective treatment option for UK MS patients The Risk Sharing Scheme itself concluded at its end that the drugs in the scheme, including Rebif, were cost-effective (based on the RSS parameters). In this subsequent NICE appraisal, real world evidence of Rebif's value has been described following more than 15 years of use of the drug by NHS patients. Additionally, Merck further reduced the Rebif price to satisfy the context in which the cost-effectiveness question is now being revisited.	Thank you for your comments. Rebif is now recommended as an option for people with relapsing-remitting multiple sclerosis. Please see section 1.1 of the final appraisal determination.

			Our conclusion on the cost-effectiveness of Rebif differs from the Committee's for two main reasons: a. In our modelling we utilise Rebif's own efficacy result from the Risk Sharing Scheme whilst the Committee instead have pooled the results of the individual RSS products. We continue to defend our position that this pooling is an inappropriate use of the RSS data. We have outlined our rationale for this previously in several documents (the original Merck submission, our response to the TAG, the resubmission in September 2017). The RSS was set up to compare individual products versus standard of care, not versus the other products (implicit in using the data in the way the Committee propose). As well as being unsound for academic reasons, this approach is prejudicial against the more effective products which will bear a disproportionally higher price impact than would be borne if they were assessed using their individual RSS result.	This appraisal compared beta interferon and glatiramer acetate with best supportive care, see section 3.2 of the final appraisal determination. In addition, the committee concluded that the use of pooled Risk Sharing Scheme estimates was appropriate. Please see section 3.14 of the final appraisal determination.
11	Company	Merck Serono	b. The Committee have chosen to follow the TAG's approach to mortality modelling rather than an alternative method which has been accepted previously by NICE in other MS submissions (TA254, TA303, TA312 and TA441). Merck provided the functionality in the TAG model in order that this alternative method could be applied to all drugs in this appraisal. We are with the Committee in acknowledging the uncertainty in modelling of this parameter, but we aren't satisfied that the Committee's conclusion about the Pokorski method is reasonable. Should its use in prior decision making be revisited?	Thank you for your comments. The committee considered the company's comments and also examined a method to model mortality rates using data reported in Jick et al. 2014. The committee preferred the approach taken by the assessment group as it was the most clinically plausible. Please see section 3.20–3.22 of the final appraisal determination.
12	Company	Merck Serono	2. The current draft recommendation is unsuitable for UK MS patients and their physicians as it restricts patient choice to a single treatment (of the six that were included in this MTA). The decision significantly limits UK patient choice and raises several fairness and equity points: • We question whether the demands for platform DMDs of 5000 new MS patients each year – who currently have the option of all six DMDs in this MTA – can be met by a single medicine. Extavia currently has <1% market share[2]; if physicians continue to elect alternative treatment options for new patients, those which we believe to be more expensive treatments – such as Tecfidera, Aubagio and Lemtrada may be preferred; in such a situation, the NHS is unlikely see any cost savings as a result of this recommendation;	Thank you for your comments. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
13	Company	Merck Serono	• By assuming that the efficacy of the non-RSS medicines is that which has been established for Avonex, Betaferon, Copaxone and Rebif via the Risk Sharing Scheme, the	Thank you for your comments. The committee

			non-RSS medicines have not been subject to the same level of scrutiny of and challenge to long-term effectiveness as the RSS products; instead they've been allowed to 'borrow' the certainty established through considerable investment by other companies and stakeholders. As a participating company in the RSS, this appears unfair to Merck. The RSS was effectively an observational study which ran from 2002 to 2016 and aside from providing access to DMDs to thousands of patients with MS and evidence on the long-term effectiveness of the participating treatments, it has also been credited with supporting the development of the MS treatment infrastructure in the UK, in part thanks to the participating companies' contributions to service development;	considered the company's comments. The committee's conclusion about disease modifying therapies is available in sections 3.10–3.15 of the final appraisal determination.
14	Company	Merck Serono	• Above we've summarised our objection to the pooling of the RSS efficacy results, but there is a related point; in assuming that the RSS efficacy results show that DMDs 'work similarly', can be pooled and can therefore be applied directly to Extavia (and other drugs) in the economic model, the Committee are also implicitly assuming that the drugs have comparable utility for patients and physicians and a comparable safety profile. This doesn't seem reasonable in light of different drug delivery mechanisms for patients and the significant variation in levels of patient support that are available through company sponsored programmes. 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. This is complemented by RebiSmart®, an electronic injection device developed to help provide easier administration for patients and to track adherence. These distinguishing features of the different treatments are lost in the assumptions in this MTA.	Thank you for your comments. The committee considered the company's comments. The committee concluded that the provision of additional support to patients would be reflected in the price of treatments. Please see section 3.27 of the final appraisal determination.
15	Company	Merck Serono	Merck has long shared the ambitions of NICE and the NHS to see continued access to the current complement of treatment options for patients with multiple sclerosis, including Rebif. This has motivated our participation in the Risk Sharing Scheme and continues to motivate our full and active engagement with the NICE process during this appraisal. We stand behind Rebif's current value proposition and - on the basis of applying what we believe to be reasonable modelling assumptions - repeat our previous conclusions that Rebif's ICER versus BSC is below the current willingness to pay threshold for the NHS. We ask the Committee to reconsider their initial decision, in light of these technical considerations and because removing all platform MS treatment alternatives except Extavia is incompatible with the clinical and cost effectiveness evidence and will result in negative consequences for MS patients and their physicians.	Thank you for your comments. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
16	Company	Novartis	Section 3.2 of the Appraisal Consultation Document (ACD) provides a list of disease-modifying therapies for relapsing-remitting multiple sclerosis (RRMS) that have been appraised by NICE since the original appraisal of beta-interferons and glatiramer acetate. *"Since NICE originally appraised these drugs, it has recommended other treatment options for relapsing–remitting multiple sclerosis including alemtuzumab, cladribine, daclizumab, dimethyl fumarate and teriflunomide."*	Thanks you for your comments. This has been amended. Please see section 3.2 of the final appraisal determination. Guidance for daclizumab has been withdrawn

			However, fingolimod (TA254; 2012) and natalizumab (TA127; 2007) are not included in the list, despite having also been appraised by NICE as treatments for RRMS. In these appraisals, fingolimod and natalizumab were recommended by NICE in specific subgroups, highly active and rapidly-evolving severe (RES) RRMS, respectively (as defined in the final guidance issued by NICE). It should be noted that daclizumab and cladribine, which are already included in the list in the ACD, are also recommended for specific subgroups of RRMS (previously-treated, active RRMS or RES RRMS, as defined in the final guidance issued by NICE). For clarity, Novartis requests that the wording of Section 3.2 be changed to include fingolimod and natalizumab to complete the list of treatments for RRMS appraised by NICE as follows (suggested changes marked in red text): *"Since NICE originally appraised these drugs, it has recommended other first-line treatment options for relapsing–remitting multiple sclerosis including alemtuzumab, ~~cladribine, daclizumab,~~ dimethyl fumarate and teriflunomide; in addition, NICE has recommended natalizumab, fingolimod, cladribine and daclizumab in specific subgroups, as defined in each appraisal."*	because the company has withdrawn its marketing authorisations for daclizumab.
17	Company	Teva UK Limited	Teva finds that the recommendations within this ACD do not form a sound and suitable base for the NHS as they would restrict access to medications for relapsing-remitting multiple sclerosis. The current availability of Copaxone (glatiramer acetate) and several beta interferons allows for patients and clinicians to choose a treatment that is most suitable for every patient, as occurred while the RSS was in operation. An FAD based on this ACD would prevent any tailoring of therapy and force all patients to have a single treatment irrespective of their specific needs.	Thank you for your comments. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
18	Company	Teva UK Limited	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, and the resulting conclusion that the RSS data for all four disease modifying treatments (DMTs) could be pooled. Teva has provided reasoning for this position in its submission (dated 29 September 2017). Teva stands by these comments and would like to add that this approach is inconsistent with previous appraisals in multiple sclerosis, where Copaxone and the individual beta interferons have been considered separately; *e.g.* the appraisals of daclizumab, dimethyl fumarate, alemtuzumab, teriflunomide and fingolimod. The Committee has been consistent with previous appraisals across a number of areas (*e.g.* disease state costs and the inclusion of carer's disutilities), but not in the consideration of a class effect between Copaxone and beta interferons. Teva considers this to be both unreasonable and unfair.	Thank you for your comments. The committee concluded that the use of pooled Risk Sharing Scheme estimates was appropriate. Please see section 3.14–3.15 of the final appraisal determination.
19	Company	Teva UK Limited	A brief recap of the points previously raised by Teva now follows, as we feel that these are still relevant and have not been sufficiently considered by the Committee. The Committee gave three reasons for its determination of a class effect: (a) that the network meta-analysis (NMA) did not demonstrate material differences between the treatments; (b) that the data	Thank you for your comments.

			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. In summary, there is no scientific basis for assuming a class effect between all four DMTs for the following reasons: • 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 pregnancy, 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 previous appraisals of DMTs for multiple sclerosis 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 <u>With specific regard to the NMA:</u> • There is no credible evidence from randomised clinical trials to prove equivalence in efficacy between Copaxone and the beta interferons o 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 o 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 o 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: o 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 of Copaxone o 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 product granted an increase in price following analysis of data	The committee considered the company's comments and noted evidence from the assessment group's network meta-analyses, which found all treatments were similarly effective compared with placebo. Please see section 3.10 of the final appraisal decision. Please see the responses to each individual issues below.

20	Company	Teva UK Limited	Selection bias Teva has undertaken additional analyses in order to address the other points raised by the Committee as justification for pooling. Firstly, the fact that the RSS was potentially subject to selection bias. Teva agrees that there is selection bias in the RSS; however, this provides justification for *not* pooling the individual DMT data, for the following reasons: • Any selectivity in patients was a reflection of normal NHS clinical practice – the specific results for Copaxone reflect its cost-effectiveness in the context of the particular clinical circumstances in which it is used in the NHS in comparison to best supportive care (BSC) (as this is what the RSS was set up to do) • 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 • Furthermore, any evidence of selection bias raises further doubts on the suitability of the recommendations within the ACD, as this would show that 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 has undertaken an analysis of the baseline characteristics of the patients on Copaxone within the RSS and those on beta interferon. The results add evidence that supports the hypothesis that the allocation of patients between Copaxone and beta interferon treatment was non-random. This analysis revealed that there were significant differences in the mean values ($p<0.05$) and the variances ($p<0.01$) for age at symptom onset ([commercial in confidence information removed]), EDSS at baseline ([commercial in confidence information removed]) and years of MS at baseline ([commercial in confidence information removed]) between Copaxone and beta interferon patients. An analysis of gender also revealed differences that were borderline significant (percentage female: [commercial in confidence information removed]; $p=0.051$). Furthermore, the RSS included some patients with secondary progressive multiple sclerosis, which is a population that is not eligible for treatment with Copaxone; this again produces a significant difference between the patient populations (percentage relapsing-remitting multiple sclerosis: [commercial in confidence information removed], respectively; $p<0.001$).	Thank you for your comments. The committee considered the company's comments and noted that it was not provided with evidence that the differences in baseline characteristics between patients receiving glatiramer acetate and the beta interferons were clinically significant. Please see section 3.14 of the final appraisal determination.
21	Company	Teva UK Limited	Switching Secondly, the fact that patients who switched treatments in the RSS were excluded from the calculation of the hazard ratio (HR) for Copaxone (as well as for the beta interferons). Teva believes that as NICE and the Assessment Group have access to the full data from the RSS, it would be straightforward to complete an analysis that included switches and, thereby, that addressed the concerns of the Committee. Teva has undertaken this analysis for Copaxone and recalculated the HR with all patients included (both switches to other RSS DMTs and to non-Scheme DMTs). This produces a HR of [commercial in confidence information removed]%, which compares to the [commercial in confidence information removed]% previously reported with switches excluded. When this	Thank you for your comments. The committee considered the company's comments. The committee noted that because comparative hazard ratio data were unavailable for the other technologies no conclusions could be drawn. Please see section

			updated value is included in the economic model using all other parameters at the Committee's preferred values, it has the effect of producing an ICER for Copaxone of £[commercial in confidence information removed] *versus* BSC. Teva feels that these calculations give the most accurate assessment of the efficacy and cost-effectiveness of Copaxone, taking into consideration the Committee assumptions and preferences. Teva has undertaken a further analysis of the switching that occurred within the RSS using the 6-year data (latest available on which this analysis could be conducted). Kaplan Meier analysis was undertaken with any switch to another DMT set as the event for each analysis and the year of switch since baseline as the time interval. This analysis revealed that the pattern of switching is both qualitatively and quantitatively different between Copaxone and the beta interferons. [commercial in confidence information removed]. These results demonstrate further distinct differences between treatment with Copaxone and the beta interferons and add further argument against the use of pooled RSS data, as outlined in the previous comment.	3.14 of the final appraisal determination.
22	Company	Teva UK Limited	Teva is of the opinion that the RSS should be used for its original purpose: to provide real world evidence of the clinical benefits and cost-effectiveness of the individual RSS DMTs against BSC (with no comparative analysis between DMTs). The data from the RSS represents the most reliable evidence for these treatments when considered individually. Whilst the pooled results give an overview of the Scheme, these results do not reflect the individual efficacy of each DMT. 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. The design of the RSS provides no scientific validity of an assumption of a class effect between the DMTs. 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.	Thank you for your comments. The committee considered the company's comments. The committee's conclusion about disease modifying therapies is available in sections 3.10–3.15 of the final appraisal determination.
23	Company	Teva UK Limited	Upon further examination of the economic model supplied by NICE, 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. Under the Association of British Neurologists' guidelines at the commencement of the RSS, a cut-off for treatment of EDSS 7 was established (equivalent to patients being non-ambulant).[1] However, at the time of establishment of the RSS there were no other DMTs available and so treatment was often continued, and this was therefore reflected in the model. However, 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. This reality was noted in the ACD where it was stated "*The committee understood that people have treatment until they can no longer walk, when they stop treatment*." Therefore, the inclusion of these costs is questionable and an artefact of the original model and does not reflect current practice, as noted by the Committee. Exclusion of these costs has a small, but meaningful effect on the ICER for Copaxone, producing a value of £[commercial in	Thank you for your comments. The assessment group implemented this change to the model in its base case and the committee accepted that treatment costs should be excluded in EDSS states 7–9. Please see section 3.26 of the final appraisal determination.

			confidence information removed] compared to £[commercial in confidence information removed] using the Committee's preferred assumptions. (The details of this oversight are as follows: within the sheet labelled 'States', on row 9 drug costs are included for EDSS states 7, 8 and 9.) **Reference** 1. Department of Health. Cost-effective provision of disease modifying therapies for people with multiple sclerosis. HSC 2002/004; 4 February 2002. Available at http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4012214.pdf [Accessed January 2018].	
24	Company	Teva UK Limited	Teva is concerned that the beta interferons are referred to by brand name in the ACD, whereas Copaxone is referred to by its International Non-proprietary Name. For consistency and clarity, Teva requests that the brand name 'Copaxone' be used. In addition, a press release on the ACD refers to communication from NICE that states that the guidance covers only branded Copaxone;[1] in which case, the brand name for Copaxone must be used to prevent misinterpretation of the recommendations from this appraisal. **Reference** 1. https://pharmaphorum.com/news/nhs-funding-five-ms-drugs-threat/ [Accessed January 2018].	Thank you for your comments. NICE normally uses generic names (British Approved Name) for drugs. References to brand name are used only when there is a need to distinguish between brands, for example distinguishing between different prices for an intervention. This approach has also been used in the final appraisal determination.
25	Company	Teva UK Limited	Pregnancy was considered by the Committee as an equality consideration. However, in the ACD it was stated that, as Copaxone was still recommended to be avoided during pregnancy, no special considerations were necessary. Teva would like to add that it is not just during pregnancy, but also when women with multiple sclerosis are considering starting a family, that Copaxone has an important role in treatment. Copaxone is currently the preferred DMT for multiple sclerosis in women wishing to become pregnant, and it can be used up until pregnancy in all cases, and during pregnancy in cases where the benefits of continued treatment outweigh the risks.[1,2] **Reference** 1. Pregnancy and birth. MS Society, London. Available at https://www.mssociety.org.uk/what-is-ms/womens-health/pregnancy-and-birth [Accessed January 2018]. 2. Copaxone (glatiramer acetate) Summary of Product Characteristics. Teva UK Limited.	Thank you for your comments. Several treatment options, including Copaxone are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee's conclusions about pregnancy are available in section 3.28 of the final appraisal determination.

26	Company	Teva UK Limited	Teva supports the proposed date for reviewing the guidance of 3 years after publication.	Thank you for your comments.
27	Company	Teva UK Limited	Teva has submitted an application through PASLU for a new Patient Access Scheme for Copaxone (both dosing regimens) with a discounted price of £[commercial in confidence information removed] *per* pack (28 days). Teva requests that this is considered by the Committee.	Thank you for your comments. The committee considered the new PAS scheme. Several treatment options, including Copaxone are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
28	Company	Teva UK Limited	With the assumptions outlined above (*i.e.* PAS price for Copaxone, Copaxone-specific RSS data with all patients who switched treatment included, and drug costs removed from EDSS states 7-9) included in the Committee's preferred version of the cost-effectiveness model, produces an ICER of £[commercial in confidence information removed] *per* QALY for Copaxone, demonstrating a strong cost-effectiveness of this treatment.	Thank you for your comments. Several treatment options, including Copaxone are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
29	Patient and professional consultee	MS Society	**Summary** We are concerned that the recommendation to restrict the number of treatments used as first line therapies could have a detrimental impact on the lives of people with MS. While we acknowledge that all of the treatments appraised are similarly effective, there are important reasons why people with relapsing MS prefer different beta interferons or glatiramer acetate over Extavia. These include a variety of reasons unrelated to efficacy but nevertheless important in ensuring people start and remain on a treatment. Reasons include mode of delivery and ease of use, side effects, storage requirements, impact on daily life and whether they are planning to start a family. Limiting the range of beta interferons and glatiramer acetate to Extavia only is likely to increase the chances of people choosing not to take any treatment at all and in turn experiencing potentially avoidable relapses and disease progression. Less people managing their MS as well as they would otherwise would will mean a greater burden on wider NHS services and carers. "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	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.

			As MS affects everyone differently people find that different treatments are better suited to their MS. Beta interferons and glatiramer acetate have been used for years as the first line treatment when taking an escalation therapy approach to treating MS. The current ABN guidelines state MS specialists may adopt an escalation approach, starting patients on a less toxic drug and only switching if this does not control their disease. Limiting the number of less toxic treatment options will result in more people choosing not to start any treatment. While many people with MS are currently taking beta interferons or glatiramer acetate, Extavia has been one of the least prescribed options within this category.[1] The low prescribing rate of Extavia is likely due to the fact that people with MS generally choose to take one of the other treatments looked at within this appraisal.	
30	Patient and professional consultee	MS Society	**Impact on people who've experienced single clinical episode** Under these recommended changes, people who have experienced a single clinical episode with multiple MRI lesions (regardless of whether they have had an MS diagnosis or not) will have their treatment options severely limited. These recommendations would mean that people diagnosed with MS who have had only one clinical episode with MRI activity will now only have the option of taking Extavia or alemtuzumab. As acknowledged in the DMT alghorithm, alemtuzumab is unlikely to be prescribed for someone who has only experienced one clinical episode, so in practice people who've experienced one relapse will only be eligible for Extavia and will have no option to switch to another beta interferon if they experience negative side effects while taking Extavia. Those people, who would have preferred to take a different beta interferon over Extavia, due to a reason other than its clinical efficacy, will most likely choose to go without treatment. This would mean a delay in starting a treatment until they have another clinical episode and therefore qualify for a greater number of treatments. This would risk their MS progressing faster than it would have if they had a wider range of first line treatment options. This recommendation would unfairly impact on this subgroup of people with MS who would have their options severely limited.	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
31	Patient and professional consultee	MS Society	**Safety profile of beta interferons and glatiramer acetate** Though less effective than some of the newer treatments now available, beta interferons and glatiramer acetate are an important option for pwMS. They offer people who are less inclined	Thank you for your comments.

[1] Redfern-Tofts, D., Wallace, L. and McDougal, A. (2016) My MS, My Needs 2: technical report

			to take risks a treatment option 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. The greater the range of DMTs available means that more people are likely to find the treatment that suits them. If these DMTs were no longer available on the NHS, it could result in less people being effectively treated for their MS. The Association of British Neurologists (ABN) specifically recommends beta interferons and glatiramer acetate for 'individuals with relatively quiescent disease'.[2] 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 by case studies gathered by the MS Society (to inform our previous submission to the MTA); several people commented on feeling most comfortable with the known risks of the more established DMTs opposed to newer, riskier DMTs. 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.[3] 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 committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
32	Patient and professional consultee	MS Society	**Mode of Delivery** The reasons different people choose to take one treatment over another are diverse and not just related to the clinical efficacy of each treatment. One of the strongest influences on why someone chooses one treatment over another is mode of delivery. When given a choice to take one of the beta interferons or glatiramer acetate, a number of people with MS have told us that the reason they chose their treatment was because it was administered less frequently. People particularly mentioned choosing Avonex because it is administered once a week, and Plegridy because it is administered fortnightly. This means that they spend less time having to think about treatment, less time self-injecting and less time dealing with side effects. As one person who has been taking Avonex for years commented: "In the absence of any other information or reassurances from NICE that the side effects of Extavia do not last anything like as long as those from Avonex, then their recommendation is	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee gave special consideration to people who may have difficulty preparing and administering

[2] 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

[3] Fox et al, Risk tolerance to MS therapies: survey results from the NARCOMS registry, Mult Scler Relat Disord. 4(3):241-9, May 2015

			more or less restricting some future patients to an interferon treatment that leaves them substantially impaired for most of the time." On the other hand, some people with MS who experience cognitive issues have told us they chose a treatment which is taken more frequently as they find it easier to remember and keep to the schedule. This reflects the variation in why people with MS choose different treatments. Another mode of delivery factor that many people with MS have commented on as an influence when choosing a treatment is the pre-filled '*straight forward pen device*' which many are self-administered with, including Rebif, Plegridy and Avonex. These developments in how the DMTs are administered show that improvements are being made to reduce the side effects and ease of use. One factor that dissuades many from choosing Extavia is that it comes in a powder form that the patient has to mix before administering, with a 44 page instruction pack Extavia is clearly not the simplest beta interferon to self-administer.[4] For people who have problems with dexterity or cognitive issues, the complicated process for taking Extavia can be extremely off putting. Without the option of easier to take treatments, many people with MS would likely need more support from a carer to help administer Extavia. 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.	Extavia when making its decision. Please see section 3.29 of the final appraisal determination.
33	Patient and professional consultee	MS Society	**Side effects** The side effects that each beta interferon and glatiramer acetate come with play a big role in influencing why someone opts for one drug over another as well as why many people switch from one to another. Side effects of beta interferons include flu like symptoms which people experience after injecting as well as unpleasant injection site reactions which lead some people to develop needle phobia. A number of people have told us that they chose Copaxone as their treatment option when they were first diagnosed as they were informed it had fewer side effects than the beta interferons.	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.

[4] https://www.extavia.com/assets/pdf/injection-training-manual.pdf

			We have also heard from people who are concerned that they will not be allowed to continue with their treatment if, due to issues such as thyroid problems, they are required to take a break. One person commented "taking any of these drugs is stressful enough without having the extra stress of removing what may have been the only drug which worked for my body". Only having the option of Extavia would likely result in many people who experience side effects having little other treatment options. This was the case with one person who told us that they had only been offered Extavia due to their MS nurse telling them it was the cheapest option and that they would only be considered for another option if Extavia proved ineffective. Not given a role in deciding which treatment they would prefer, this person had a negative experience with Extavia due to side effects, commenting: "It made me feel worse, more dizzy etc so only lasted 3 months on it. A neurologist even thought I was suicidal when I said I felt better having nothing than that injection".	These recommendations are not intended to affect people having treatment that was started in the NHS before the guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them until they and their NHS clinician consider it appropriate to stop. In addition, treatment should be given in line with the marketing authorisation of each treatment. Please see section 1.5 of the final appraisal determination.
34	Patient and professional consultee	MS Society	**Innovation** In paragraph 3.2 the committee highlights that 'its remit was to revisit the original appraisal, and to compare to beta interferons and glatiramer acetate with best supportive care, rather than the newer drugs'. However, in paragraph 3.25 the committee reports that while the treatments may be considered innovative compared with best supportive care, they are not when compared to the newer treatment options and therefore should not be considered innovative. This argument 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.	Thank you for your comments. The committee considered the consultee's comments and determined that the treatments were innovative compared with best supportive care when they became available on the NHS. Please see section 3.30 of the final appraisal determination.
35	Patient and professional consultee	MS Society	**Copaxone's use during conception and pregnancy** Currently Copaxone is the only licensed treatment for relapsing MS which is not contraindicated for pregnancy and is often chosen by women who are planning to start a family. The argument put forward in the appraisal consultation document that 'special considerations' shouldn't be applied for Copaxone due to the marketing authorisation suggesting that it is preferable to avoid taking during pregnancy ignores the evidence from both people with MS and their clinicians.	Thank you for your comments. Several treatment options, including Copaxone, are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.

			We have heard from neurologists who have expressed particular concern over this aspect of the recommendation highlighting that they regularly prescribe Copaxone to women who are planning a pregnancy as the risk of not taking a treatment at all outweighs the risks involved in taking Copaxone while pregnant. As it is not contraindicated in pregnancy, the judgement on the risk involved, is down to women with MS and their neurologist, the committee should not be making this judgement on their behalf. NICE should listen to the judgement of neurologists who regularly make decisions with their patients on whether Copaxone is safe to take when pregnant and breastfeeding. Women with MS who are planning a family in the near future have written to us to express their concern over this recommendation. They highlight that they are aware of the risks involved in taking Copaxone while pregnant but that they are more concerned over the risk of going without treatment for a long period: "I am very disheartened to hear that NICE might decide to stop this treatment, as I understand Copaxone is the only medication that is ok to take - although I understand there are risks to any medication taken in pregnancy....with a more severe RRMS, I am quite worried about completely stopping all treatments, especially during the pre-pregnancy bit, and if it takes many months to conceive". We have been contacted by women who plan to switch from treatments such as dimethyl fumarate to Copaxone while they try to start a family. The committee's recommendation that Copaxone does not deserve special consideration goes directly against Copaxone's licence and general prescribing practice in England and Wales and should be reconsidered.	The committee's conclusions about pregnancy are available in section 3.28 of the final appraisal determination.
36	Patient and professional consultee	MS Society	**Pharmaceutical company support** The appraisal consultation document makes no mention of the extra support given by some of the pharmaceutical companies to help people take their products. If Extavia is the only option for new patients we would want to see that they are given the same level of support that those who are already taking one of the other beta interferons receive. While Extavia may be the most cost effective option does this factor in the 24 hour nurse support phone number that some of the other treatments provide?	Thank you for your comments. The committee considered the consultee's comments. The committee concluded that the provision of additional support to patients would be reflected in the price of treatments. Please see section 3.27 of the final appraisal determination.
37	Patient and professional consultee	MS Society	**Lifestyle factors** Lifestyle factors for people with MS are often a big reason why they choose one treatment over another. The storage requirements of these different treatments mean that people find one is a better fit around their daily life. For example a cold chain is less essential when taking Plegridy, which makes it a more practical choice for people who need to travel a lot	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is

			such as people with MS who serve in the military. More frequent injections that need to be stored in a refrigerator make it difficult for people to travel. A number of people have commented to us that they simply stopped going abroad while taking beta interferons as they found it too much hassle. Compared to many of the treatments approved more recently by NICE, beta interferons and glatiramer acetate have less burdensome monitoring requirements, with 6 monthly blood tests for the former and none for the latter. This can be a factor in why people choose one of these treatments: "I still work, I cannot afford to be off work with side effects of some of the other medication. I didn't want to have to attend regular blood tests as required for some drugs I had a choice of. I felt that with the minimal effect on my body that this medication would suit me best."	important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
38	Patient and professional consultee	MS Society	**Impact on newer appraisals** We would like to see some consideration over what impact this could have on the appraisals which have taken place since 2002 which have used beta interferons and glatiramer acetate as a comparator. Would newer appraisals have to go to reappraisal? This would cause a great level of concern for people with MS currently on these treatments.	Thank you for your comments. Please see the NICE guide to the processes of technology appraisal 2018 for information on the procedure for review of NICE guidance. Any review proposal is subject to a 4-week consultation period involving appropriate consultees and commentators.
39	Patient and professional consultee	MS Society	**Lack of transparency** We do not feel that the basis for this decision has been transparent. The recommendation of the appraisal consultation document sees all of the treatments as of a similar efficacy, and therefore base's its decision on the cost effectiveness of each option. As cost effective analysis is not provided within the document we are unable to make an argument as to whether more treatments than Extavia are cost effective. The discussions with pharmaceutical companies over the price of their products have also not happened in the public domain and we are unable to scrutinise these decisions. While the risk sharing scheme has been used as the key data for this appraisal, the final results are still yet to be published, this is another reason why the decision to provide Extavia alone is not as transparent as it should be. It is unclear to us why NICE and the Department	Thank you for your comments. Full details of the cost-effectiveness analyses cannot be published in the public domain as this would allow commercial discounts provided by the companies to be back-calculated. Data from the Risk Sharing Scheme were made available from the data

			of Heath have not made this data available to the public and we would like to know why this decision has been made.	owners (Department of Health and the companies participating in the Risk Sharing Scheme). It is the responsibility of the data owner to release the data.
40	Patient and professional consultee	MS Society	These recommendations will also unfairly impact on people who: - Have a history of seizures and shouldn't be offered beta interferon but can be offered glatiramer acetate - Are unable to swallow tablets and will have their first line treatment range reduced to Extavia and Alemtuzumab only.	Thank you for your comments. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
41	Patient and professional consultee	MS Society	We would also like to know how this recommendation would impact people who are currently taking one of the restricted treatments but are required to have a break for some reason. Would they be required to start Extavia instead despite having been taking one of the other options previously?	Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. These recommendations are not intended to affect people having treatment that was started in the NHS before the guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them until they and their NHS clinician consider it appropriate to stop. In addition, treatment should be given in line with the marketing authorisation of each treatment. Please see section 1.5 of the final appraisal determination.

42	Patient and professional consultee	Multiple Sclerosis Trust	**Summary** **We strongly believe that all current treatments should remain available as a treatment option for all eligible patients.** • **We consider that the proposal to recommend Extavia alone is discriminatory towards those for whom problems with dexterity, vision and cognition form part of their disability (see 3.1).** • **We consider that the proposal to recommend Extavia alone is discriminatory towards women of childbearing age who intend to conceive, as it will remove all appropriate treatment options (see 3.6).** This decision has been made without reference to clinical practice or experience and ignores significant real-world differences between each of the beta interferons and glatiramer acetate. We are particularly disappointed that this recommendation does not acknowledge individuality and would take away choice from people with MS. NICE has acknowledged that all six drugs are equally effective at reducing the number of relapses and slowing down disability progression. The decision to approve Extavia and not the other five drugs is based on the cost of the drugs; Copaxone and the other beta interferons are more expensive than Extavia. No consideration has been taken of the potential impacts on people with MS and on specialist MS services or the costs of these impacts. The MS Trust's expertise lies in understanding and representing the perspectives of people with MS and ensuring that people have access to effective treatments. We invited comments on the ACD from people affected by MS and from health professionals. Over 500 people with MS and over 100 specialist MS health professionals (26 neurologists, 73 MS specialist nurses, 5 MS specialist therapists, 4 pharmacists) responded to our survey; their feedback has informed our response to the ACD and is provided in the appendices to this document. In both surveys, 98% of respondents disagreed with the NICE recommendations, and many gave explicit examples to explain their response. We urge you to look at our supporting appendices to see what people with MS and specialist MS health professionals have said about the recommendations.	Thank you for your comments. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. Individual issues raised are addressed in the responses below.

43	Patient and professional consultee	Multiple Sclerosis Trust	**Importance of beta interferons and glatiramer acetate in the current treatment pathway** Because of the unique circumstances of this multiple technology appraisal, the committee is in the position of appraising six drugs which have been prescribed by the NHS for more than fifteen years. The drugs are established treatments with well-defined safety profiles. MS teams are very experienced with these agents; there is a wealth of published research and clinical experience confirming their general safety; there are well-established services to initiate and monitor treatment. Despite the availability of alternative oral treatments since 2014, the beta interferons and glatiramer acetate continue to be prescribed widely. Extensive real-world experience of these agents has confirmed that at an individual patient level, different products suit different individuals. There are significant differences between the drugs in terms of ease of use, dosing schedules, storage, side effects, safety during pregnancy and tolerability. These factors impact on different people to a greater or lesser extent, and individuals will have personal preferences which enable them to effectively manage their treatment. 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. Shared decision making is a priority for the NHS and has become an important component of helping patients to choose the disease modifying drug which is right for them. Approving Extavia alone and withdrawing the remaining beta interferons and glatiramer acetate will severely limit the potential for MS teams to share the decision process and find a treatment that is right for the individual and their circumstances. 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[5]; for many people, their MS has remained stable while taking one of these 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; others who have started with one of the oral treatments have experienced side effects and switched to one of the beta interferons or glatiramer acetate. The impact on patient care of approving Extavia alone and withdrawing the remaining beta interferons and glatiramer acetate should not be overlooked. Our comments focus on the following major issues: • impact on people with relapsing MS • impact on MS services	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.

[5] Scolding N, et al. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. Practical Neurology 2015;15(4):273-279.

			• overarching criticisms of the appraisal	
44	Patient and professional consultee	Multiple Sclerosis Trust	**Impact on people with relapsing MS** The differences between each of the beta interferons and glatiramer acetate have a significant impact on people with MS, this has not been taken into account by NICE in reaching this decision. In pooling the data from the RSS, which excluded Extavia, the differences between the drugs was not apparent; yet the impact of this real-world difference on patient adherence should not be overlooked. Dosing schedules, storage, side-effects and tolerability vary greatly between the drugs and we have reports of people who have had bad experiences on a particular drug, which leads to non-adherence. Non-adherence on a particular drug because of a bad experience, can also lead to disillusionment with MS treatments in general. Evidence demonstrating the value of treating people with MS early is compelling, and therefore if people refuse treatments this can lead to poorer health outcomes and increased disability, which increase the demand for services and therefore costs to the NHS. Our own research and that of the MS Society shows that Extavia is the least prescribed of the six modifying drugs under consideration[6]. In our HP survey, 11% of respondents commented that all treatments except Extavia were offered by their MS team; 9% of respondents commented that Extavia was offered as an option but no one on their caseload was taking it. In our survey of people with MS, just 0.4% (2/522) indicated that they had taken Extavia. Particular issues around ease of use, injection frequency and other factors are explored below, demonstrating why this is the least preferred of the options.	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
45	Patient and professional consultee	Multiple Sclerosis Trust	**Ease of use** **We consider that the proposal to recommend Extavia alone is discriminatory towards those for whom problems with dexterity, vision and cognition form part of their disability.** All of the drugs under evaluation, with the exception of Extavia and Betaferon, are provided as ready-to-use injection devices. Extavia is supplied as solvent and powder which must be made up each time it is taken. The Patient Information Leaflet for Extavia **details the seventeen step instructions** for doing this: www.medicines.org.uk/emc/files/pil.6529.pdf. For the MS Decisions resource we	Thank you for your comments. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee gave special consideration to people who may have difficulty

[6] MS Trust. Evidence for MS specialists: findings from GEMSS. Letchworth: MS Trust; 2016
MS Society. My MS, My Needs 2016: access to treatment and health care. London: MS Society; 2016

			prepared a video which shows how the injection is made up https://youtu.be/bxyMMa2vNHA and injected https://www.youtube.com/watch?v=Q0_RopyN66w). People with manual dexterity, visual or cognitive difficulties, all of which are common problems in MS, will find this very difficult, if not impossible, to do. Those with fatigue or busy lives will also struggle to make up and inject Extavia every other day. 13% (70/522) people with MS responding to our survey mentioned ease of use as a major criteria for choosing an injectable disease modifying drug. People with MS: *They should try mixing Extavia with gloves on. Hopefully they will realise how difficult it can be for people with reduced dexterity due to lack of sensation in finger tips.* *Smaller needle albeit three times a week, came already filled, I could and still self-inject especially as I have dexterity issues meant didn't have to faff about and do it myself swiftly and easily. Still the case as I live by myself.* *I take Avonex and chose this drug because you inject with an easy to use pen once a week.* MS specialist: *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.*	preparing and administering Extavia when making its decision. Please see section 3.29 of the final appraisal determination.
46	Patient and professional consultee	Multiple Sclerosis Trust	**Injection frequency** The drugs under evaluation are self-injected at different intervals, from daily to once a fortnight. Injection frequency is one of the most important factors in treatment choice, with daily, weekly or fortnightly frequencies being most popular. Extavia is injected every other day, a pattern that is not easily remembered. Over a two week period, patients are injecting on a different day of the week, which increases the risk of simply forgetting to do an injection and consequently losing therapeutic effect. Ultimately, it increases the risk of relapses, of someone discontinuing treatment altogether and in the longer term acquiring greater disability due to relapses or progression. More frequent injections lead to a higher incidence of injection site reactions, increasing the need for hospital visits to deal with infected injection sites and increasing the risk of discontinuing treatment. Patients are instructed to rotate injection sites; with less frequent injections, there is more opportunity for an injection site to recover before it is used again.	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.

			20% (103/522) people with MS responding to our survey mentioned injection frequency as a major criteria for choosing an injectable disease modifying drug. People with MS: *Only having to manage the injection every two weeks means that any side effects are limited to every other weekend and have not impacted on my ability to work full time.* *I chose Avonex initially as injection was weekly and the least invasive to my life. The same decision I made when swapping to Plegridy which was a fortnightly injection.* *I am considering Plegridy as it is once a fortnight and the side effects appear manageable.* MS specialists: *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.* *People choose the other injectables for a variety of reasons e.g. less frequent injections.* *Extavia has the same efficacy as the other injectables, but is not chosen by people with MS as it is difficult to remember to take it being on alternate days. We now have more people on Plegridy and Copaxone. The former because of the less frequent administration and the latter due to its lack of side effects profile.*	
47	Patient and professional consultee	Multiple Sclerosis Trust	**Side effects** People often experience flu-like symptoms after each beta interferon injection. These can be severe and are a major reason why people stop taking one of these drugs. Every other day injections required for Extavia make it particularly difficult to manage the impact of flu-like symptoms on work and family life; less frequent dosing schedules such as weekly or fortnightly make it possible to plan injections at a time (for example over the weekend) when flu-like symptoms will have less impact. Glatiramer acetate does not cause flu-like symptoms and is often a preferred option for this reason. Other disease modifying drugs are associated with side effects which are a significant concern for some and influence choices made by neurologists and patients. Dimethyl fumarate carries the risk of a serious brain infection, alemtuzumab leads to thyroid problems and there is an increased risk of birth defects in women taking teriflunomide. Some side	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee was aware that some treatments were associated with a higher

			effects make drugs unsuitable for people with pre-existing conditions, for example gastrointestinal side effects make dimethyl fumarate unsuitable for people with gastritis or inflammatory bowel syndrome. The severely restricted list of drugs that would be available as a result of this ACD will make it much more difficult for MS specialists and patients to choose a suitable treatment based on side effect profile, either at treatment initiation or, more importantly, treatment switching. People with MS: *Extavia worked fine until I was too bruised and skin hardened so injection liquid started coming out again. Switched to Tecfidera, but am having problems with side effects still after half a year, so don't know what to switch to now.* *Copaxone, despite having one possible nasty side effect, appealed to me because it would not leave me with flu-like symptoms and needing to take additional medication to combat it*. *Based on thinking through options available chose Copaxone as it did not cause flu symptoms on injection days.* *I felt flu like side effects during the night of administration, and sometimes the next day, which is frustrating, but it is ok as it is only one day per week.* *Didn't want side effects from meds daily.* *Rebif was one of the less "invasive" drugs - by that I mean the side effects were less serious than that of stronger drugs such as Tecfidera. Plus, it was recommended by my neurologist. As I had a low white blood cell count and digestion issues we felt Copaxone would be the best drug for me.* MS specialists: *I can foresee patients having to transfer onto a more expensive drug after failing on Extavia rather than trying an alternative injectable. They will then be forced to choose one of the oral drugs and accept their associated risks and monitoring even if this impacts upon their daily life and causes anxiety regarding possible severe side effects.* *The side effects should be considered - an injection of interferon every other day is less tolerated than an injection every two weeks or glatiramer acetate every day. Cost-effectiveness should include the costs of managing side effects and the effect of side effects on employment.*	risk of specific adverse events. The committee saw no evidence to suggest that the risk of stopping treatment because of adverse events was different between treatments . Please see section 3.10 of the final appraisal determination.

48	Patient and professional consultee	Multiple Sclerosis Trust	**Severely limited choice** With this recommendation, NICE is proposing that treatments available to people with active relapsing MS would be: interferon beta 1b (Extavia), teriflunomide (Aubagio), dimethyl fumarate (Tecfidera) and alemtuzumab (Lemtrada). Teriflunomide, dimethyl fumarate and alemtuzumab are each associated with side effects which may make them unsuitable, particularly for those with comorbidities or those who are risk averse. People taking one of these first line treatments may experience an adverse event such as liver injury or prolonged lymphopenia and be unable to continue taking the drug. They will have greatly limited choice if Extavia is the only injectable treatment available to them, with the risk that they may not take up or may discontinue treatment entirely. 16% (82/522) people with MS responding to our survey raised the issue of severely limited options if Extavia was the only injectable disease modifying drug. 26% of health professionals responding to our survey specified concerns that the decision limited patient options. MS specialists: *People who require first line treatment and cannot tolerate the oral medications will have limited options.* *Limited choice. Extavia is more difficult to tolerate than some of the other injectables.*	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
49	Patient and professional consultee	Multiple Sclerosis Trust	**Drug safety monitoring** The proposed first-line treatments require more frequent blood and urine tests to monitor for potential side effects. For many people, this will mean a visit to a hospital clinic which is often disruptive for family and work commitments and can involve significant travel costs. Glatiramer acetate is often preferred as no safety monitoring is required. This minimises the impact of the treatment on family and work commitments. In addition, the focus of health professionals to manage the increased monitoring requirements impacts on people with MS who may have to wait longer for review appointments or when experiencing a relapse. 2% (9/522) people with MS specifically cited lack of monitoring on Copaxone as reason for choice People with MS: *It [Copaxone] suited my lifestyle. No monitoring, wouldn't get in way of my job.*	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.

			I chose Copaxone because I was in full time work and it was simple, no significant side effects and no need to take time off work for blood tests.	
50	Patient and professional consultee	Multiple Sclerosis Trust	**Use of treatments during conception and pregnancy** **We consider that the proposal to recommend Extavia alone is discriminatory towards women of childbearing age who intend to conceive, as it will remove all appropriate treatment options.** The committee rejected equality considerations concerning safety of glatiramer acetate during pregnancy based on the wording of the marketing authorisation. The committee will be well aware that the wording used is routinely hypercautious. There is now substantial data to show that glatiramer acetate can be taken safely during pregnancy, reflected by the fact that this is now well-established in clinical practice. As noted by a neurologist responding to our survey: "The exclusion of Copaxone would be a particular loss to women wanting a safe disease modifying drug during pregnancy - for which this drug is now routinely used in some centres." The proposed first-line treatments Extavia, teriflunomide, dimethyl fumarate and alemtuzumab all carry significant risks during pregnancy and are contraindicated. 3% (14/522) people with MS responding to our survey raised the issue of conception and pregnancy as a consideration when choosing an injectable disease modifying drug. 17% (20/122) of HPs responding to our survey raised the issue of conception and pregnancy as a consideration when choosing an injectable disease modifying drug. People with MS: *First of all, the worst decision would be rejecting Copaxone. As far as I know it is the only drug for people with not very active MS that can be taken while pregnant or breastfeeding.* *Upset. 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.* MS specialists: *These recommendations are a harmful retrograde step in the management of patients with MS. They completely remove from patients the ONLY licensed treatment with evidence of safety during pregnancy (copaxone). Because of this I consider the recommendation to be discriminatory on the grounds of gender.*	Thank you for your comments. Several treatment options including Copaxone are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee's conclusions about pregnancy are available in section 3.28 of the final appraisal determination.

51	Patient and professional consultee	Multiple Sclerosis Trust	**Impact on MS services** **Greater costs for NHS and social care systems** Many people are not happy with the higher risks and possible side-effects associated with the proposed first-line treatments for relapsing MS. Faced with a choice between frequent injections and the flu-like side effects of Extavia and the higher risk side effects of these treatments, many people will choose no treatment. This is likely to lead to increased burdens on the NHS due to the more rapid progression of MS – e.g. more GP and consultant appointments; more time needed with specialist nurses; greater pressure on social care and family care systems; more unplanned hospital admissions etc. MS specialists: *Limiting the options to one drug is likely to limit uptake of treatment at this stage, which may have implications for future disease activity and disability.* *It may result in short term savings but is likely to increase long term costs with treatment failure and escalation.* *Absolutely shocking decision that will cause disabling and distressing relapses resulting in an increase in the need for symptom management, rehab, social care and benefits.*	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
52	Patient and professional consultee	Multiple Sclerosis Trust	**Patient care** People who struggle with manual dexterity, visual or cognitive issues will require additional support from MS services to manage their treatment. In addition, the drug monitoring requirements of the proposed alternatives impact on the health professionals who support people with MS. The time taken to carry out the higher level of monitoring will increase the pressure on an already overstretched workforce. As a result, other patients may have to wait longer for appointments or the costs of additional staff to manage the workload will be incurred. MS specialists: *More clinic time for reviewing and possible administration due to poor dexterity.* *We would get an increase in calls, patient visits and a lot of complaints.*	Thank you for your comments. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee gave special consideration to people who may have difficulty preparing and administering Extavia when making its decision. Please see section 3.29 of the final appraisal determination.
53	Patient and professional consultee	Multiple Sclerosis Trust	**Lack of Patient Support Programme**	Thank you for your comments. The committee noted the consultee's

			Extavia has a very limited patient support programme. This will put extra pressure on the MS nurses to train people when they start injecting and support them when they have problems with side effects or injection technique. MS specialists: *Many patients cannot do this [make up treatment] and cannot rely on others to do it. I am sure that GP services would be unable to accommodate alt[ernative] day injections being administered, nor could the district nursing teams. Within MS we teach a self-management approach to wellbeing and the choice of drugs has been an integral part of this, it helps with adherence to medication, I truly believe that we reduce wasted medication costs to the NHS when taking into account choice of DMD.* *They would not get the support that the other drug companies offer (nurse support package).* *Novartis DO NOT provide training demo kits for patients any more. So we cannot train our patients!* *If Extavia became the only therapy option for RRMS, we would be unable to continue supporting patients at home with Injection training and follow on support and care. This would have a huge impact on the MS Specialist Nurses who would then have to train all patients in their clinics resulting in a huge increase in their already overburdened workloads.*	comments. The committee concluded that the provision of additional support to patients would be reflected in the price of treatments. Please see section 3.27 of the final appraisal determination. Several treatment options are now recommended, including those from companies providing additional patient support programmes. Please see sections 1.1–1.3 of the final appraisal determination.
54	Patient and professional consultee	Multiple Sclerosis Trust	**Increased demand for oral treatments** The decision to recommend Extavia alone will increase demand for teriflunomide, dimethyl fumarate and alemtuzumab. This will place increased pressure on over-stretched services in order to initiate treatment, provide side effect management and drug safety monitoring. MS specialists: *I can foresee patients having to transfer onto a more expensive drug after failing on Extavia rather than trying an alternative injectable. They will then be forced to choose one of the oral drugs and accept their associated risks and monitoring even if this impacts upon their daily life and causes anxiety regarding possible severe side effects.*	Thank you for your comments. The committee noted the consultee's comments. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination
55	Patient and professional consultee	Multiple Sclerosis Trust	**Management of patient expectations** Specialist MS teams will need to deal with the problem of treating patients who will be offered different treatments according to the date their MS was diagnosed which will add to the complexity of managing disease modifying drugs within the MS service. Health professionals will need to explain the lack of treatment options to newly diagnosed patients, placing them in potentially upsetting and difficult positions and ultimately leading to increased pressure on	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with

			services. It may also lead to lower staff morale, as specialist teams will be unable to offer what they consider as better or more appropriate treatment options, and will be unable to provide high standards of care due to increased workload. MS specialists: *I think many MS people would be unhappy due to side effects etc., and would be calling in for assessment and advice which would ramp up pressure to our already stretched out services.* *I feel this is very poor judgement on NICE's part. By limiting the options to patients you are causing wider problems in the long term. NICE continually recommends treating patients as individuals and tailoring their care to them then proceeds to offer a 'one treatment fits all' approach. This WILL have a negative impact on drug compliance, reduce patients' options when they have a reaction to extavia and put over-whelming pressure on a delivery service that already messes up orders.* *Medications that are already a reminder of having MS need to fit in as seamlessly as possible with someone's life for them to feel comfortable with it, for them to be accepting of side effects and for them to stick with it. I think there are very likely to be more switches to other treatments and therefore ultimately cause disruptions to patients and add to the workloads of already stretched services.* *The most important thing is being able to offer people with MS choice of treatments so as we can work collaboratively to find the most effective treatment that they can tolerate, administer with least effort and minimal if any side effects. We can only do this if we have the range available.*	MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
56	Patient and professional consultee	Multiple Sclerosis Trust	**Overarching criticisms of the appraisal** **Lack of transparency** The proposal to recommend Extavia alone is based on cost-effectiveness. However, as the ACD states, the drug costs are 'commercial in confidence'. This means that stakeholders and members of the public are not able to evaluate the most important issue governing the Committee's decision to approve Extavia and reject the remaining five drugs. It is also unclear to what extent the manufacturers have been able to participate in negotiations over patient access schemes and discounts. None of these discussions have been conducted in the public domain.	Thank you for your comments. Full details of the cost-effectiveness analyses cannot be published in the public domain as this would allow commercial discounts provided by the companies to be back-calculated.
57	Patient and professional consultee	Multiple Sclerosis Trust	**Best supportive care** NICE has compared the cost of the beta interferons and glatiramer acetate with best supportive care, and found Extavia alone is cost effective. No details are given of what would	Thank you for your comments.

			constitute "best supportive care". The MS Trust and other stakeholders have raised the issue of best supportive care as a comparator in previous single technology appraisals: it has been rejected as a comparator because (1) it is not an option in current clinical practice, (2) the concept is idealistic because in reality people with MS often have very limited access to services, (3) there is no consensus on what best supportive care is and how much it costs, and (4) it is inconsistent to compare the cost of a disease modifying drug which has a constant cost regardless of location with a comparator which would vary locally since there is no mechanism to ensure that best supportive is consistently implemented. Moreover, in reality, those people for whom Extavia is not appropriate (for reasons outlined above) would instead be offered either teriflunomide, dimethyl fumarate or alemtuzumab. Assessing the beta interferons and glatiramer acetate against best supportive care may have been appropriate when the original TA32 appraisal was carried out more than fifteen years ago, but the committee will know that the treatment landscape for relapsing MS has moved on dramatically since that time. For the purposes of understanding the true cost to the NHS of decisions made in this appraisal, the drugs should be compared to the current, alternative treatment options people will actually be offered; best supportive care is not one of these. Recent single technology appraisals have acknowledged this new treatment paradigm and have made decisions based on cost effectiveness compared with active treatment (dimethyl fumarate TA320, teriflunomide TA303, alemtuzumab TA312). Comparison with best supportive care unfairly disadvantages beta interferons and glatiramer acetate in this appraisal.	The committee was aware that it has recommended other treatment options for relapsing–remitting MS but noted that its remit was to revisit the original appraisal and compare beta interferons and glatiramer acetate with best supportive care rather than the newer drugs. Please see section 3.2 of the final appraisal determination. The committee's conclusions about the modelling of best supportive care are available in section 3.18 of the final appraisal determination.
58	Patient and professional consultee	Multiple Sclerosis Trust	**More costly alternative treatments** Those people for whom Extavia is not appropriate would instead be offered one of the other "first line" drugs - either teriflunomide, dimethyl fumarate or alemtuzumab. These drugs are more costly and require more safety monitoring than beta interferons and glatiramer acetate; the net effect of the ACD decision will be greater cost to the NHS.	Thank you for your comments. The committee noted the consultee's comments. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination
59	Patient and professional consultee	Multiple Sclerosis Trust	**Innovation** Section 3.2 of the ACD states: The committee understood that its remit was to revisit the original appraisal, and to compare beta interferons and glatiramer acetate with best supportive care, rather than with the newer drugs. Section 3.25 states: The technologies are no longer considered innovative.	Thank you for your comments. The committee considered the consultee's comments and determined that the treatments were innovative compared with best supportive care when they became available on the NHS. The committee

			By comparing the drugs to best supportive care, the alternative treatment option which applied at the time that TA32 was undertaken, but on the other hand refusing to recognise the innovative nature of the treatments which applied at the time that TA32 was undertaken, the appraisal committee is employing double standards. When compared to best supportive care, all of the treatments under appraisal should be considered innovative. Since TA32 was carried out, both Avonex and Rebif have been reformulated to improve their tolerability and immunogenicity. There have also been significant enhancements in the autoinjectors for these two beta interferons which greatly improve patient adherence and therefore clinical efficacy. Although Plegridy has been included in the review of TA32, it is actually a new product, using pegylation to extend circulating half-life and therefore reduce injection frequency making it an attractive option for patients. Finally, Copaxone has been reformulated to provide an alternative dosing schedule, three times weekly in addition to the daily injection frequency. In contrast, there has been limited development of Betaferon and Extavia. Long-term commitment to developing and improving a product should be considered when making this recommendation.	noted that the benefits of ease of preparation and administration conferred by auto injection devices were not captured in the cost-effectiveness analysis. Please see section 3.30 of the final appraisal determination.
60	Patient and professional consultee	United Kingdom Clinical Pharmacy Association (UKCPA)	We are concerned that this recommendation will have an impact on medicines adherence due to a reduction in patient choice. The wide range of injectable products currently available offer patients the option of different frequency of injection (daily to once a fortnight), route of injection and device all of which in this patient group and for patients with long term conditions have a large impact on medicines adherence. Extavia only provides the option of alternate day administration. If this is the only option is it likely that patients will tend to choose one of the other first line options that have easier dosing schedules, which would have a cost impact to NHS England. From practice Extavia is one of the lesser used options because patients prefer the devices for the other beta interferons.	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
61	Patient and professional consultee	United Kingdom Clinical Pharmacy Association (UKCPA)	We are also concerned that removing glatiramer acetate completely from availability will have a significant impact on patients. Glatiramer acetate currently is the disease modifying drug of choice in patients who are planning pregnancy, an important consideration for a large group of patients with relapsing remitting multiple sclerosis. It also has a better side effect profile, reduced monitoring requirement and tolerance for many patients compared with interferons and some of the other first line Disease Modifying Therapies (DMTs).	Thank you for your comments. Several treatment options, including glatiramer acetate, are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.

				The committee's conclusions about pregnancy are available in section 3.28 of the final appraisal determination.
62	Patient and professional consultee	United Kingdom Clinical Pharmacy Association (UKCPA)	Glatiramer acetate has recently been made available as a generic product which is likely to provide a cost saving for NHS England	Thank you for your comments. The committee was aware that glatiramer acetate is now available as a generic product (Brabio). Glatiramer acetate is now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
63	Patient and professional consultee	UKMSSNA	We strongly support the view that patients are informed which is the cheapest injectable Disease Modifying Therapy (DMT) but should not be denied access to other drugs that may suit them better due to frequency of administration, provision of a prefilled auto injector, drugs not requiring regular monitoring blood tests and the profile of adverse effects. Adherence to the medication is likely to be affected if patients do not have a DMT that most suits them with regards to the above points.	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
64	Patient and professional consultee	UKMSSNA	We are concerned that this recommendation will affect directly those patients wishing to conceive, 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, which has recently been reflected in the Summary of Product Characteristics. Denying patients the option to use this medication if wishing to conceive could put them at higher risk of a relapse and developing permanent disability during this time period. The option of using Copaxone has particularly been useful for some patients who needed to stop their oral treatments in order to try to conceive.	Thank you for your comments. Several treatment options, including Copaxone, are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee's conclusions about pregnancy are available in

				section 3.28 of the final appraisal determination.
65	Patient and professional consultee	UKMSSNA	We are concerned that this recommendation removes patient choice who often make their decision on how it will effect there lifestyle such as ease of administration, frequency and side effects. In addition to this some may have difficulty with manual dexterity and cognition which may affect their ability to administer the injection independently. This directly goes against Government policy on the patient being at the centre of their care. Extavia is more complex to administer as it requires preparation prior to administration. If people have no input into the decision making they are less likely to adhere to the treatment. Also people may decide not to start treatment therefore putting themselves at greater risk of further relapses and increased NHS costs Copaxone has consistently better tolerated compared with B-IFNs and oral DMDs. This is borne out by individual centres data and the risk sharing scheme data.	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee gave special consideration to people who may have difficulty preparing and administering Extavia when making its decision. Please see section 3.29 of the final appraisal determination
66	Patient and professional consultee	UKMSSNA	We are concerned that this recommendation will directly affect people with epilepsy who are advised not to use interferons therefore denying access to Copaxone affects prescribing for this group of patients.	Thank you for your comments. Several treatment options, including Copaxone, are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
67	Patient and professional consultee	UKMSSNA	We are very concerned that this recommendation only affects care in England hence creating a backward step to pre Risk Sharing Scheme where postcode lotteries determined treatment. How can this be explained to patients?	Thank you for your comments. For information on implementation of appraisal guidance please see section 4 of the final appraisal determination.

68	Patient and professional consultee	UKMSSNA	We are concerned that this recommendation will impact significantly on MS Services, Extavia (Novatis) do not provide Nurse training or a Nurse Support line for the product therefore local services will have a greater demand for training, injection side effects, support for users etc. this will ultimately affect adherence to the product reducing cost effectiveness totally	Thank you for your comments. The committee noted the consultee's comments. The committee concluded that the provision of additional support to patients would be reflected in the price of treatments. Please see section 3.27 of the final appraisal determination. Several treatment options are now recommended, including those from companies providing additional patient support programmes. Please see sections 1.1–1.3 of the final appraisal determination.
69	Patient and professional consultee	UKMSSNA	We are concerned that this recommendation has not taken into account that it is rare that a patient chooses extavia/betaferon when shown all the injectables. The main reasons for this is that it is not prefilled, the storage is bulky, the autojector is poor, and if a patient has manual dexterity problems then they are unable to do the injection. A range of DMT's is imperative to enable nurses to work with individuals to find the preparation that bests suits them for dexterity, tolerability, lifestyle	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee gave special consideration to people who may have difficulty preparing and administering Extavia when making its decision. Please see section 3.29 of the final appraisal determination.

70	Patient and professional consultee	UKMSSNA	We are concerned that this recommendation lacks consideration given to the varying side effects and the patients' tolerability of these side effects which is different for every individual. Unlike the B-IFNs, copaxone does not produce NABs.	Thank you for your comments. The committee was aware that some treatments were associated with a higher risk of specific adverse events. The committee saw no evidence suggesting that any treatment had a significantly higher rate of adverse events. Please see section 3.10 of the final appraisal determination.
71	Patient and professional consultee	UKMSSNA	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. Reducing the choice of medication will ultimately increase the blood monitoring burden on already over stretched services with a potential for serious untoward incidents resulting in patient harm.	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
72	Patient and professional consultee	ABN	**INTRODUCTION** This revision from the previous assessment report proposes a significant change from current practice, and a significant shift from the apparent conclusions of the last consultation document (August 2016). The drivers to the changes appear to be: 1. a final determination of a threshold willingness to pay / QALY – still not explicitly declared but met by only one product offered at an undisclosed price to the NHS 2. a decision to exclude CIS from the review, including all the studies done in patients with CIS who would now be classified as having early relapsing-remitting MS. It should be	Thank you for your comments. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee was unable to make recommendation for treating clinically isolated syndrome because the diagnostic criteria for

			noted that in the previous modelling of CIS patients, the cost per QALY for this group was well below NICE's usual threshold **CONSEQUENCES** The consequences of these recommendations, if adopted in their current form will be: 1. drug naïve patients looking to start IFN/GA will be offered Extavia as the only option, using the Extavia autoinjector or manually injecting. The only available regimen for a first-line injectable will be alternate day subcutaneous injections. 2. patients switching within first-line therapies for reasons of tolerability will have Extavia as the only injectable option 3. patients already switched to an oral therapy from an injectable for reasons of tolerance, but failing to tolerate that therapy, will have Extavia as their only injectable option (the recommendations do not allow a patient to go back onto their previous therapy unless it was Extavia)	multiple sclerosis and clinically isolated syndrome has changed. The committee's conclusions on clinically isolated syndrome are available in section 3.4–3.5 of the final appraisal determination.
73	Patient and professional consultee	ABN	**AMBIGUITY** The recommendations in this document for using Extavia are: • the person has relapsing–remitting multiple sclerosis or • the person has secondary progressive multiple sclerosis with continued relapses The marketing authorisation for Extavia is: • the treatment of patients with relapsing-remitting multiple sclerosis and two or more relapses within the last two years • the treatment of 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 • They are also licensed for the treatment of 'patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses'. There is ambiguity in the wording of the recommendations –making some commenting difficult. "RRMS' as currently defined (MacDonald criteria 2017) will include many patients in	Thank you for your comments. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee was unable to make recommendation for treating clinically isolated syndrome because the diagnostic criteria for multiple sclerosis and clinically isolated syndrome has changed. The committee's conclusions on clinically isolated syndrome are available in section 3.4–3.5 of the final appraisal determination.

			the single demyelinating event category of the marketing organisation. The structure of the consultation document is consistent with the committee considering these to be “CIS” as previously defined. We would need clarification on how NHSE (and equivalents elsewhere) might interpret this wording to extend/ restrict current prescribing practice. No stopping criteria are proposed.	
74	Patient and professional consultee	ABN	**CHOICE** The position of members of the ABN prescribing for people with MS is that it is in patients’ interest to have the widest choice of available therapies. This reflects >15 years of experience using these drugs. Immediate consequences of implementation of these recommendations would be: 1. A reduction in choice for drug naïve patients starting first line therapy or switching within level. The current choices allow patients a variety of routes (sc/ oral/ im), injection frequency (from daily to once/fortnight) and of side effect profile. All drugs are currently used across the UK, with Extavia having the lowest usage. Other products have been favoured with more accessible injection devices, a lower frequency of injection, preferred patient support programmes and the lack of need for fresh mixing of the product prior to injection. The interferons are not suitable for patients with a paraprotein. The current pattern of usage, evolved over years of shared decision making and patient/ HCP interaction in the absence of financial constraint, has shown Extavia to be the least used of the first line injectables in the UK 2. For a patient whose response creates equipoise on escalation or switch within level, the only choice now available will be to switch to a more expensive oral or infusible medication, with other injectables no longer available. 3. There will not be a first line therapy with a marketing authorisation for use through pregnancy, removing the option of treatment through pregnancy for women of child bearing age. The current alternative would be to use an intermittent monoclonal – a difficult decision given the risk profile of currently available drugs in his group The result of these proposals will be a marked reduction in choice for patients within this level of treatment. Despite the advent of oral medication, many patients still choose an injectable, in part due to their long safety record and well established risk/benefit profile. The MS therapeutic community have widely adopted the principles of shared decision making (with widespread use of the MS Decisions website and now the MS Trust MS Decision Aid). Our adoption of this practice has been in line with core NHS principles. Reduction in the choices to patients as the net result of this work would be a retrograde step. The likely outcome will be higher use of the first line orals (dimethyl fumarate and teriflunomide) where a cheaper injectable might have been chosen.	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee’s conclusions about pregnancy are available in section 3.28 of the final appraisal determination.

75	Patient and professional consultee	ABN	**INEVITABLE OBSOLESCENCE AT TIME OF PUBLICATION** Generics are not mentioned, with glatiramer acetate assumed to be Copaxone at its current price. The advice appears already obsolete if it does not reference, by whatever methodology is used, the price that would allow access of a glatiramer acetate into the UK health system. The EMA have accepted Brabio as "glatiramer acetate" and generic substitution is likely to be accepted. The timing of this advice from NICE, coming out at the same time as potential tendering for generics to be adopted to regional formularies, underlines the potential impossibility of attempts to apply NICE's usual procedures to drugs at the end of their patent. By excluding "glatiramer acetate" the proposals might actually exclude a drug that is more cost-effective (at the price at which it will soon be offered) than Extavia.	Thank you for your comments. Several treatment options, including glatiramer acetate are now recommended. The committee was aware that a generic version of glatiramer acetate is available to the NHS. Please see sections 1.1–1.3 of the final appraisal determination.
76	Patient and professional consultee	ABN	**RETROSPECTIVE NATURE OF PROCESS AND ROLE OF RSS** The set-up of the UK RSS was an extraordinary event. It required a step of faith by the four companies involved, risking their product's reputation and pricing model internationally to allow access of the drug to UK patients. A binding *a priori* analysis scheme was accepted and, even when changed, the companies, in good faith, accepted the revised year 4 onwards analysis plan as devised by the Scientific Advisory Group. The final 10 year results, available to NICE, essentially validate the initial pricing decisions, with a deviation score of <10% for the drugs in aggregate. This was based on an agreed 20 year time horizon with a willingness to pay £36 000/QALY. All four companies remained committed to the scheme to its conclusion and contributed to the set up and support of MS services under the terms agreed. As a result of the scheme, the UK price for these drugs is below the rest of Europe, and considerably lower than the free market price in the US. The 20 year model and £/QALY threshold used to determine the entry price of each drug were based on NICE procedures at the time of the drug launch. The current time horizon extension of 50 years is a welcome evolution, reflecting the time course of MS, but the change in willingness to pay/QALY is a post-hoc development 15 years into the widespread use of these drugs in the UK. There would appear to be a case for basic fairness to allow the companies who stayed with the scheme to continue with the RSS price as initially modelled, in keeping with the spirit of combined risk taking which underpinned the enterprise. A unilateral shift in goalposts at this point risks jeopardising future schemes of this nature in the UK. Those who remember the dire situation at the outset, where the UK was at risk of being the only developed country to be unable to offer these innovative therapies, continue to appreciate the courage the UK Departments of Health and companies displayed at the inception of the scheme. The manufacturers of the proposed sole drug to be available, Extavia, played no part in the scheme and did not contribute to the collection of the data which has underpinned the drugs'	Thank you for your comments. Several treatment options, including are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee's discussion of the Risk Sharing Scheme is available in sections 3.11–3.15 of the final appraisal determination.

			efficacy and allowed the cost efficacy to be estimated. This seems an unfair outcome of the scheme.	
77	Patient and professional consultee	ABN	LACK OF APPLICABILITY TO CURRENT PRESCRIBING PRACTICE A major flaw in the modelling, inevitable given the timing of this appraisal after later generation drugs have been launched, is the assumption that patients discontinue at fixed rate per annum independent of response. This is not a new technology launching in an empty space. The current use of these drugs is generally targeted towards people with milder early disease. Patients are closely monitored clinically and radiologically and non-responders are rapidly moved onto other therapies. As such, the poor responders pulling down the results will simply not continue on these drugs. Only patients who have a good early and sustained response will be left on this level of therapy. Although analysis of the RSS included an attempted "ITT" analysis to explore this, the late age and disease stage of starting patients within the scheme and the lack of suitable escalation therapies for the majority of the epoch of the scheme leave this question unaddressed.	Thank you for your comments. The committee's conclusions on rates of stopping treatment are available in section 3.23 of the final appraisal determination.
78	Patient and professional consultee	ABN	**EFFECT OF EXCLUDING THE MORE FAVOURABLE CIS MODELS** We appreciate the issue of CIS is difficult due to changing definitions. NICE produced cost effectiveness models for the use of these drugs in CIS in the last appraisal document offered for consultation. The models showed the drugs assessed to be cost effective when started at the stage of CIS. In early studies, using the Poser criteria, CIS will have referred to patients with a single clinical attack regardless of MR activity or CSF findings, becoming "clinically definite MS' only with a second attack. The 2001 McDonald criteria (just coming in at the initiation of the RSS) allowed a diagnosis of RRMS with a new MR lesion distant from the first clinical attack. In the 2010 McDonald criteria, patients previously classified as CIS but with simultaneous enhancing and non-enhancing lesions on an initial scan would be classified as RRMS, and in the 2017 revision, CIS with oligoclonal bands and >2 lesions in the right places, even without evidence of different aging, are now also classified as RRMS. These changes have the effect of converting most patients in traditional "CIS" studies into patients with early MS, and "time to CDMS" is simply the time between two clinical attacks. As such, these studies may best be seen as treatment trials in early MS. What is striking is the consistently higher rate of relapse reduction treating MS at this stage, and the improved performance of these drugs in NICE's modelling when used early in the disease, rather than waiting to the point of 2 relapses in 2 years, in itself now a marker of relatively active MS. Leaving out this early treatment data has the effect of demonstrating limited efficacy of the drugs when used in an RSS-like cohort (mean age 39, disease duration 9 years). Real world	Thank you for your comments. The committee was unable to make recommendation for treating clinically isolated syndrome because the diagnostic criteria for multiple sclerosis and clinically isolated syndrome has changed. The committee's conclusions on clinically isolated syndrome are available in section 3.4–3.5 of the final appraisal determination.

			studies and personal experience has already resulted in a shift in prescribing patterns in the UK to an earlier, younger group. These recommendations will have the result of preventing demonstrably cost effective practice of early prescribing by using unmatched data from late prescribing. It is not clear why this large piece of work by NICE has not been used to inform the final advice.	
79	Patient and professional consultee	ABN	**POTENTIAL UNDERMINING OF NEWER DRUGS' MODELS** We acknowledge that the use of these drugs has fallen in recent years, being replaced for reasons of efficacy and tolerability by newer oral drugs and monoclonals. We recognise that the cost effectiveness models of these newer drugs is modelled on the RSS price of the first line injectables. As a community, it might be possible to create algorithms for treatment of MS which do not allow for new prescriptions of the 5 products excluded by these recommendations, but this appraisal in isolation offers no insight into what the implications may be for the availability of the newer drugs. It would be impossible, as an organisation, for the ABN to accept the adoption of these proposals without modelling of the knock-on effect on the availability of the drugs on which we are currently rely. This reflects the very unusual situation of NICE appraising a technology freely available for 15 years whose historic economic modelling underpins several generations of new technologies.	Comment noted.
80	Public	Patient	Shocking idea. Copaxon has a very good safety profile and works in a different way than other treatments. Not everyone needs to get on newer unsuitable treatments (Lemtrada etc) This would significantly limit the choice for patients and would dramatically limit their quality of life.	Thank you for your comments. Copaxone is now recommended as a treatment option. Please see section 1.2 of the final appraisal determination.
81	Public	Patient	I am very concerned about the potential decision to remove these drugs from use within the NHS, having taken 2 of these treatments I am still able to work as a nurse and believe these drugs are important in maintain health & delaying disability in many young people. Please reconsider.	Thank you for your comments. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
82	Public	Patient	I am emailing with my views about the proposal to stop offering newly diagnosed MS patients Rebif, Betaferon, Avonex and Copaxone. I was diagnosed with CIS in January 2017 with a high chance of conversion to MS. I started on Rebif in February. However, I've stopped this recently due to low wbc and am awaiting bloods and review in 2 months. Will my neurologist	Thank you for your comments. Several treatment options are now recommended.

			be able to restart Rebif or offer an alternative? What are the proposed treatment options planned for CIS patients who are only eligible for the DMTs that will be withdrawn?	Please see sections 1.1–1.3 of the final appraisal determination. The committee was unable to make recommendation for treating clinically isolated syndrome because the diagnostic criteria for multiple sclerosis and clinically isolated syndrome has changed. The committee's conclusions on clinically isolated syndrome are available in section 3.4–3.5 of the final appraisal determination.
83	Public	Patient	I use plegridy - this means that I suffer fly like symptoms once every fortnight. I effectively lose a day out of every 14. I manage this by Injecting on a Sunday as this enables me to rest. If I had been forced to have Extavia instead I could suffer these side effects every other day thus making it impossible for me to work. For this reason I absolutely believe plegridy should remain available to patients with MS	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. Plegridy is no longer being considered as part of this review (ID809) and will be considered in a separate Single Technology Appraisal.
84	Public	Patient	Currently take Copaxone & have have had no relapses. Very short sighted decision based purely on cost, not benefit. Very disappointed that a treatment I started very recently.	Thank you for your comments.

				Copaxone is now recommended as a treatment option. Please see section 1.2 of the final appraisal determination.
85	Public	Patient	NHS England are again putting patients at risk by even contemplating this ridiculous idea. The costs of MS Sufferers being admitted to hospital every few weeks/months after relapsing will far outweigh the cost of the drugs and the potential further strain on hospital services as well as leaving people at risk of disability and death. You are playing Russian roulette with people lives. MS Patients are already denied treatment in England due the NHS England refusing to fund Savitex to help with neuropathic pain. Strange how the other UK health trusts fund this but England can't. Let's stop this selective process for health and welllbeing.	Thank you for your comments. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
86	Public	NHS Professional	It is fair to say all the interferons are 'more alike than different' so making extavia the default and first line treatment makes sense economically. However it seems odd to lump Glatiramer (GA)in with this issue, as although it is similar efficacy to IFN, the side effect profile and mode of action is very different, so there are clearly going to be patients who for various reasons get on better with GA; removing this as an option seems illogical. You could also argue this for some of the IFNs which are significantly different in formulation eg Plegridy. Note an unintended consequence of this restriction would be an increase in use of oral first line DMT's, as well as extavia, eg aubagio and tecfidera, which are both MORE expensive than IFN & GA. I assume the purpose of this exercise is to set up a negotiating position for the companies to reduce current list prices to the NHS, which is fair enough.	Thank you for your comments. Several treatment options, including glatiramer acetate, are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
87	Public	Patient	I have been on plegridy for over one year now I feel it has given me my life back so far no relapse (I have RRMS) I am disgusted that you would consider this, there are bound to be other ways to save money on the NHS. This is a debilitating progressive disease which there is NO CURE as of yet. This is disgusting that you could do this to us all you wouldn't dream of taking the funding from drug addicts or people with alcohol issues or people who have never paid into the health service because some of which just couldn't be bothered get out of bed and actuall seek employment. You would never stop treatment for cancer patients so why MS patients. Why not stop people from other countries that just come specifically to use our FREE NHS why not crack down on that. I'm begging please don't stop our treatments I for one want to be able to play with my grandchildren PLEASE reconsider . don't take this away from us.	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. Plegridy is no longer being considered as part of this review (ID809) and will be

				considered in a separate Single Technology Appraisal.
88	Public	Patient	I just cannot understand why this is being proposed.It's playing god with people.What needs to be sorted is the ridiculously high prices the drug companies charge.Are you saying the neurologists that recommend them for patients don't know what they're doing.Surely it would have been flagged up before now if they weren't beneficial.You're penalising the wrong people who need it.People who have paid into the system all of their working life.Faceless people who don't have an inkling or a care about who this affects.Save money job done! People will end up having relapses then go back into hospitals putting yet more strain on our crippled NHS	Thank you for your comments. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
89	Public	Patient	I am a young woman, diagnosed 5 years ago with Rapidly Evolving RR MS. I am currently taking DMD (Fingolimod). I am considering trying to become pregnant soon, and glatiramer acetate would have potentially been a drug I was looking into as recent evidence has been published which appears to suggest that it is safe to take during pregnancy. 1) Has all of the relevant evidence been taken into account? I do not believe this paper has taken into account the recent evidence of the change in safety guidelines for glatiramer acetate in pregnancy and the recent change in EU legislation regarding its pregnancy category. To the best of my knowledge the paper does not properly evaluate the risks and benefits in pregnancy of glatiramer acetate vs other interferon - especially compared to the proposed alternative Extavia which is not recommended in pregnancy. 2) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? I do not believe that the summary take account of the costs involved in higher risks to pregnancy and the cost to the NHS of managing MS in pregnancy and the cost of care to the neonate in the case of a relapse during the later stages of pregnancy. Including whether or not there could be greater risk of prematurity if the mother is unwell, and the cost to the NHS associated with that. 3) Are the recommendations sound and a suitable basis for guidance to the NHS? I do not think the recommendations are sound and suitable guidance to the NHS for women of childbearing age wanting to become pregnant. 4) Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race,	Thank you for your comments. Several treatment options, including glatiramer acetate, are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee's conclusions about pregnancy are available in section 3.28 of the final appraisal determination.

			gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? YES This guideline appears to discriminate against women of childbearing age, and against pregnancy and maternity. I think the guideline could also be considered to be discriminatory against disability attributed to MS, by preventing a young women from enjoying the right to participate in creating a family (purely on the grounds of needing medication, and having to take something which is not suitable in pregnancy, when there is a pregnancy safe alternative available - glatiramer acetate) given that her peer, who is not disabled by MS, is able to enjoy this benefit. Creating a family has benefits to a women in other areas as well, often improving mental health, self esteem and giving purpose in life which results in reducing other costs to the NHS. I believe it would be wrong for NICE to stop this treatment form being available. Although I understand there are risks to any medication taken in pregnancy, with a more severe form of RR MS, stopping all DMDs, especially during pre-pregnancy and for the months is takes to conceive, could be disastrous for the long term health and outcome of the women. I hope this is taken into consideration, even if copaxone was only licenced for women of childbearing age who might become pregnant.	
90	Public	Patient	It angers me that NICE would consider restricting access to any disease modifying therapy for newly diagnosed MS patients. As someone who was diagnosed just two years ago, I know the importance of having access to these drugs and being able to choose between them. I was put on Copaxone 18 months ago after careful consideration of all the side effects the drugs could cause (this consideration included Avonex (interferon beta-1a), Betaferon (interferon beta-1b), Plegridy (peginterferon beta-1a), Rebif (interferon beta-1a) in addition to Copaxone (glatiramer acetate). I chose Copaxone because it seemed it would interfere the least with my work as an orchestral musician and I have tolerated it well. It is essential that patients can choose from a list of appropriate medication or it will prevent them from leading normal, active lives. I am also very concerned that NICE are restricting access to Copaxone when it is the one disease modifying therapy that has been proven safe to administer during pregnancy. It highly discriminates against young women who may be considering having a family in the future. They must be granted access to this drug when they are initially diagnosed so that	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options, including Copaxone are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.

			their options for motherhood are not limited and do no involve an unpleasant transition between medications. This proposal must not ever take effect!	
91	Public	Public	This propsal is very concerning due to the points below ; 1. the lack of choice for the patient 2. The impact on patient lifestyle, in particular those who work full time 3. the fact that the proposed drug cannot be guaranteed safe from viruses like CJD. Please consider these details when reviewing	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
92	Public	Patient	I have had MS for 37 years. I have been taking Avonex since 1998 as this is proving successful for me. Writing as a patient, I would ask NICE to consider the importance of having the widest possible range of treatment options available for medical teams to discuss with their patients. Many of the MS appropriate treatments each only benefit a certain percentage of patients and therefore the widest range of availability is key. Otherwise it is discriminating against patients who may only benefit from one of the treatments being proposed for withdrawal.	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
93	Public	NHS Professional	As a medical practitioner but more in this case as a good friend of a MS sufferer it seems unhelpful to be so restrictive with treatment options. My friend needed to try a number of the agents examined until one suited him in terms of side effects that allowed him to continue to work full time. Patients and Doctors need choice not a one size fits all approach. As from life and clinical practice no two people or patients are the same. Different options often need to be tried to maximise someone's quality of life.	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.

94	Public	Patient	I do not understand the reasoning behind removing affective drug options for people with MS? Every patient is different and some are more tolerant to some medications than others. Also tolerances to side effects can change. So what happens when this side effects are too much for a patient? Should they just put up and be grateful for getting anything? Life with MS is hard and the future is uncertain. Having treatment options withdrawn for what appears to be financial reasons will end up costing more for care, hospital admissions, doctors appointment and inability to work, pay taxes etc. Please reconsider this desicion.	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
95	Public	Patient	As a sufferer of relapsing remitting multiple sclerosis fortunate enough to have been prescribed plegridy I find this document an outrage. Though on their face the interferons appear to be the same, not all are suitable for the individual making the choice to take them as a first line therapy - and of all the interferons chosen by NICEas recommended, it would seem the most old fashioned and intrusive version of this therapy of all will be placed at the fore; it has to be mixed, risking needle stick injury, and then injected - not everyone is dextrous enough to accomplish this, fear of needles notwithstanding; it is intrusive - it has to be given 3 times a week compared with Plegridy and Avonex, given fortnightly. In short, it is a cheap, short sighted and dangerous therapy that is not always suitable for some patients. The withdrawal of the interferons from frontline treatment seriously deprives those incapable of taking the stronger therapies offered deprives the new patient of choice. It is a sad day when, patients who read of therapies such as plegridy or avonex or even betaseron go to their neurologist in the knowledge that there are few other therapies in existence that will help them with this debilitating and crippling disease, knowing that they will not be able to get any further help. Is it fair and reasonable not only to deny the patient this choice, but to effectively tie the hands of neurologists who have strived for years to build a satisfactory pharmacology that can be of help to their patients? Aret you determined to send neuroinflammatory care back to the dark ages, when nothing whatsoever could be done for sufferers? The fight to obtain interferon as a therapy for MS was a long and hard one Please don't restart it in the name of cost effectiveness, when so many people - as yet undiagnosed - will come to rely on the choices among this group for their future wellbeing.	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee gave special consideration to people who may have difficulty preparing and administering Extavia when making its decision. Please see section 3.29 of the final appraisal determination. Plegridy is no longer being considered as part of this review (ID809) and will be considered in a separate Single Technology Appraisal.

96	Public	NHS Professional	We look after 3000 patients with multiple sclerosis at our Trust. Copaxone is clearly required as it is the only DMT that has a licence (2017) to be administered in pregnancy and breast feeding. This does not apply to the beta-inteferons. MS is dominantly a younger female disease. In our Trust we have no experience of Extavia. It has not been the preference of our patients with MS over the last decade. It is surprising that there were no neurologists on the sub-panel which put this out to consultation	Thank you for your comments. Several treatment options, including Copaxone, are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee considered evidence submissions from patient and professional bodies and heard from clinical experts during committee meetings. Please see the committee papers.
97	Public	NHS Professional	The different interferon devices and formulations available give the patients the opportunity to choose the one that fits better their lifestyle, increasing adherence. Extavia® manual device is a SC preparation that has to be reconstituted. Many of our patients have problems with dexterity in their hands, so I don't think these patients are capable of doing this. Not all the patients can tolerate all the interferon preparations. The adverse reactions are different in between the formulations; therefore by simplifying this to one preparation will eliminate treatment choice. Examples: Eg 1: Extavia® is given alternative days, so some patients might not have enough time to recover from flu-like symptoms or skin reactions in between doses. A real patient example: I had a patient with low platelets with Plegridy but not with Avonex. Another example: SC preparations and IM preparations do not have the same skin adverse reactions. For some patients this is not interchangeable. Copaxone® is the only drug available for the treatment of RRMS that is not contraindicated in pregnancy and breastfeeding. When women are breastfeeding (after birth) is when they are at more risk of relapse. Copaxone® is the only drug available for the treatment of RRMS which does not affect FBC, LFTs and U&Es. Copaxone® is very often prescribed when Tecfidera® or Fingolimod® is not an option due to lymphopenia.	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options, including Copaxone, are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee gave special consideration to people who may have difficulty preparing and administering Extavia when making its decision. Please see section 3.29 of the final appraisal determination.

			For those patients that are needle phobic Extavia® manual device is not a choice, since the needle is exposed. Other preparations such as Plegridy® have the needle covered. Rebismart® is an option for those patients that forget to take the medication or have careers, since the device has an alarm and tells you when the last dose was administer.	
98	Public	Patient	I am an RRMS sufferer diagnosed in 1991. I have been on Avonex since 2003/2004. It took me many years to get the drug, which back in the 90's was the drug to be taking in order to slow symptoms of the disease. I was completely incensed when I heard NICE were considering doing away with this and other Disease Modifying Drugs DMD's. I have not relapsed for the last 6 years and I believe Avonex has helped with this. People suffering with MS haven't chosen to have MS. It is a severely disabling disease, for which no two days are the same. An MSers life is seriously compromised. I have worked alongside a colleague, who has now passed away due to the effects of MS and know other people who have suffered as a result of having this awful disease. My point is this: a) Pharmaceutical Companies should not be allowed to continue selling these DMDs at such a high price. If they develop and market a new DMD that proves to be successful, then the cost of older products should be made cheaper b) It's obvious that this is an NHS cost cutting exercise at the expense of over 100,000 people's welfare. I would like to know if NICE have viewed this proposal from this angle? An MSer is taken off one of the named DMD and given a cheaper DMD. That MSer then relapses because that DMD wasnt so good. That MSer is seen by an MS Specialist Nurse and a Specialist and requires hospitalization for steroid treatment. This would then utilize a hospital bed and the varios nursing staff to monitor this patient. Steroid treatment is normally one week. I know - I've been through it a number of times! Is Option b) cheaper than leaving an MSer on their current DMD that is working for them? Multiply this by the number of MSers currently taking one of the named DMDs in your proposal. Your choice!! Signed: A Very Unhappy MSer	Thank you for your comments. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
99	Public	NHS Professional	I am extremely concerned that patient choice will be restricted to just one agent out of the interferons and glatiramer acetate. There is likely to be individual variation in the side effect profiles for each agent and this is not considered in the report. If the patient cannot tolerate Extavia then other options (IFN or GA) of similar efficacy cannot be considered if this appraisal is finally approved. This can only have a detrimental effect on patient care and choice.	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is

			Regarding Clinically Isolated Syndrome (CIS). This is still a very relevant sub-group which should be considered within the remit of the appraisal. The report states that " The diagnostic criteria will soon be revised again, which may mean that clinically isolated syndrome as currently defined will cease to exist." This is factually incorrect. The most recent guidelines (Thompson et al, Lancet Neurology, Dec 2017) still keeps clinically isolated syndrome as a distinct entity. If guidelines evolve and change every 1-2 years then when will the committee ever be able to consider clinically isolated syndromes? The potentially earlier diagnosis of MS after a single clinical episode (CIS) raises another issue regarding the indication of Interferon Beta or Glatiramer Acetate. If MS is diagnosed in a CIS patient after cerebrospinal fluid oligoclonal band analysis or enhancing brain/cord lesions on magnetic resonance imaging, then what implications does this have on eligibility for first line injectables? If the diagnostic label changes to MS then do they need to have two attacks in two years to qualify? Whereas beforehand, if they were felt to have CIS with high risk of conversion to MS (e.g. on radiological grounds) they would qualify for Interferon-beta. So would they no longer qualify just because they have been diagnosed MS after a single relapse?	important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee was unable to make recommendation for treating clinically isolated syndrome because the diagnostic criteria for multiple sclerosis and clinically isolated syndrome has changed. The committee's conclusions on clinically isolated syndrome are available in section 3.4–3.5 of the final appraisal determination.
100	Public	Patient	I have relapsing remitting MS (first symptoms in 2010, diagnosed in 2012) and I have been taking Copaxone since 2013. I am very upset that Copaxone will no longer be available for newly diagnosed RR patients, whilst I understand that this will not affect my access to the drug it is beside the point. Copaxone has a different mechanism from the interferon-beta drugs and I don't understand why it has been appraised alongside them. Copaxone has minimal side affects and has allowed me to lead a full life. I have continued to work full time - I don't need to worry about flu like symptoms or taking medication which could potentially make me feel worse than my actual MS symptoms. Whilst I know Copaxone does not have any effect on disease progression whilst Extavia might, at the stage in my life when I was diagnosed (34 years old) I needed to have the confidence that I was taking a drug that I knew would not affect my fertility or my ability to work at a key point in my career but nevertheless would offer some mitigation against having a relapse. I have not experience any relapses since I began taking Copaxone and the minimal impact it has had my life has actually allowed me to often forget that I have MS. I would ask NICE to reconsider this decision based on the fact that Copaxone does not produce flu like symptoms (and indeed any Copaxone side affects are minimal after the first year) and importantly it is also safe for women to take during pregnancy if necessary - neither of which is covered off by Extavia.	Thank you for your comments. Several treatment options, including Copaxone, are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.

101	Public	Patient	Today, as a new patient, I began treatment with Avonex. I was astonished to be told by the training nurse of this NICE proposal, the adoption of which would seem incredibly harmful to the welfare of MS patients in England. One reason multiple Interferon-beta formulations are offered is that some patients react badly to particular formulations. A second reason is that patients can expect to develop some immunity to the treatment over time, necessitating a change of formulation. What can these patients do if only one formulation is offered, to which they react, or to which they develop antibody resistance? It leaves them without a treatment option, a ridiculous state of affairs when the medical community has worked hard over the years to broaden the available options to the current state. Restricting treatment options will inevitably lead to a statistical average decline in health for MS patients, which will place a financial and logistical strain on hospital services that otherwise wouldn't be present. This proposal doesn't even make sense judged on the accountancy metric that seems to have inspired it.	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
102	Public	Patient	I am sending you my comments on the recent report and recommendations of NICE on the use of interferons for MS patients.First, some comments on the report itself. As an MS sufferer I find it somewhat difficult, if not offensive, to recognise the reports description of MS: Symptoms can include pain, disturbance to muscle tone including weakness or spasticity, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment This is a massive and quite unjust under-statement. 'Can include pain and disturbance to muscle tone - etc'! Last December we buried my Aunt who had spent the previous 15 years in a nursing home, totally bed bound and incontinent, and unable to be fed anything other than semi-liquid foods. Before entering the home, her husband (my uncle) had spent 10 years or more as a more or less full time carer. Similarly, an old friend of mine, in his early sixties, died of MS following a similarly traumatic experience of the disease. Similarly later the reports states that: 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	Thank you for your comments. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee considered evidence submissions from professional bodies and patient groups and heard evidence from patients regarding the impact of multiple sclerosis during the committee meetings. The quality of life of carers was considered as part of the economic model used to determine cost-effectiveness of the treatments. Please see

			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. This too is a massive understatement and underestimation of the impact of MS on patients and carers. Perhaps I have been somewhat unlucky, but my Uncle, referred to above, fell into deep depression and committed suicide after years of trying to help my aunt, only to witness the unrelenting progress of MS. MS sufferers might well question the NICE process and whether or not the process and associated panels were fully informed of the nature, impact and unrelenting progress of MS! My other main point, however, is the report's more or less total absence of any references to the side effects of the various interferon treatments. I currently use Avonex (which I note will continue to be available to current users). I have been using Avonex for some 8 years or so and even now and with the use of Paracetamol and ibuprofen, I experience significant side effects in the form of a headache, general aches, fatigue and difficulty in concentrating on any one task or topic for more than 15 minutes or so. While the severity of these side effects varies from week to week they can last 24-36 hours, leaving me not able to do much for a day or so. I notice that side effects from Extavia (to be injected every other day) are reported in terms that sound similar to Avonex. In the absence of any other information or reassurances from NICE that the side effects of Extavia do not last anything like as long as those from Avonex, then the recommendations concerning interferons could more or less restricting some future patients to an interferon treatment the side effects of which could leave some patients substantially impaired for most of the time. I also wonder if and how the side effects were taken into account in the calculations of QALYs and urge NIE to provide information and explanations on this. I would also welcome confirmation from NICE that the side effects of Extavia are minimal in intensity and duration for all users, and will not impact on their working, family and personal life to any significant extent. Unless NICE can provide evidence of this then I am very much of the views that the recommendations concerning the use of Extavia and the removal of other interferons as DMDrugs for MS should be rejected	section 3.24 of the final appraisal determination. The committee was aware that some treatments were associated with a higher risk of specific adverse events. The committee saw no evidence suggesting that any treatment had a significantly higher rate of adverse events. Please see section 3.10 of the final appraisal determination.

103	Public	Patient	I believe the proposals by NICE will have appalling consequences for anyone suffering from the very complex effects of MS. I was diagnosed in 2010 and it was a shock, I felt lost and I didn't know what to do. The MS Society, my MS Nurse and Neurologist not only educated and calmed me, but they gave me choice. Choice of how to deal with the diagnosis, choice of medication, choice of when I wanted to start and choice if I didn't feel comfortable with the medication I was taking etc. I didn't feel pressurised into taking one sort of medication or another and I felt in charge of when I would like to start medication and what I wanted to take. I can never fully explain how important that was, and still is, to me. My MS nurse spent a long time going through all the options available and it right that I was able to make a choice that suited me best. I started taking Avonex and if I didn't feel comfortable with it or it had adverse effects, I would be able to change it until I found the right one. The proposal by NICE would take that away and that is fundamentally wrong. An MS diagnosis is something that it incredibly difficult to deal with anyway and now having to worry that you don't have access to the medication that suits you the best or now being too scared to try another medication incase you would want to change back and can't, is something that will be devastating to many MS sufferers and yet to be diagnosed people. Please give people the choice they deserve to get the medication that's right for them and for it not to become just another cost-cutting exercise and country lottery, which will have devastating consequences and far-reaching effects. Thank you, [redacted]	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.
104	Public	Public	I write in objection to proposed recommendation 1.2 in the National Institute for Health and Excellence (NICE) appraisal consultation document (issued December 2017) concerning beta interferons and glatiramer acetate for treating multiple sclerosis. The recommendation states: Glatiramer acetate, Avonex and Rebif (both interferon beta 1a), Betaferon (interferon beta 1b) and Plegridy (pegylated interferon beta 1a) are not recommended within their marketing authorisations as options for treating multiple sclerosis. Implementation of this recommendation would result in an unacceptable reduction in the range of disease modifying treatments (DMTs) in the 'moderate efficacy' category available	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination.

			through the National Health Service (NHS) for new patients with MS (pwMS). For new patients, Extavia (interferon beta-1b) would be the only DMT in this category available on the NHS. According to the appraisal consultation document this recommendation has been proposed for reasons of cost-effectiveness on the basis that these treatments "work similarly". While the DMTs may "work similarly", the efficacy, the related side effects and the lifestyle impact of the consumption regimes of each of these drugs vary considerably. It is critical that pwMS have choice of treatment options, particularly given the wide range of symptoms pwMS can experience and that patients' tolerance for risks in treatment is varied. Side effects are widely recognised as a barrier to effective treatment. Preventing pwMS from selecting which DMT works best for them vis a vis side effects will have a measurable negative impact on the management of MS in the United Kingdom. Currently, the UK has one of the lowest prescribing rates for MS DMTs in Europe and it is gravely concerning that rates would likely fall further as a consequence of a reduction of patient choice such as the one proposed in the NICE appraisal consultation document. It also concerning that the NHS could fall further behind the standard of best practice operating in comparable jurisdictions. It is noted that all the DMTs the recommendation proposes removing from the NHS are available to pwMS in Australia under the General Schedule of the Australian Government's Pharmaceutical Benefits Scheme. The views of key stakeholder organisations on the issue of diverse treatment options are clear. The Multiple Sclerosis Society UK has advised diversity "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" and "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." The Multiple Sclerosis Trust, meanwhile, argues "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".	The committee was aware that some treatments were associated with a higher risk of specific adverse events. The committee saw no evidence suggesting that any treatment had a significantly higher rate of adverse events. Please see section 3.10 of the final appraisal determination.

			While the cost effectiveness of treatments must be a consideration in the delivery of a sustainable NHS, it is paramount that the NHS continue to provide patients with treatment options. The reduction of DMTs in the moderate efficacy category from six to one is unacceptable and not in the best interests of pwMS. While all the DMTs should be retained on the NHS for new patients, there should at least be a minimum of three available to patients. I urge the appraisal committee to recognise the importance of patient choice at its fourth meeting on 6 March and remove (or revise) recommendation 1.2 in the final version of the document. Yours sincerely, [redacted]	
105	Public	Patient	As the people who this decision will impact on have not been diagnosed yet, how have they been consulted? I see that two MS charities have been consulted, however there are other organisations and web forums that could reach this groups of people as well as those that are newly diagnosed. The timing (just before Christmas) and short length of this consultation suggests that there is not the appetite to fully consult with potential and current patients. I would expect this to be challenged if I ran a consultation in this way in the (NHS) organisation that I work for. At the very least, it is poor practice. I was diagnosed with MS in 2016. With the support of my consultant I chose to go on glatiramer acetate. I chose this over the beta interferons as a first line treatment mainly because I work full time and didn't think I would be able to continue doing this if I was also dealing with flu like side effects. This has worked well for me so far. My main MS symptom is fatigue so I am able to continue working full time with some home working as an adjustment. There is a potential economic impact of this proposal. While the treatments may have the same efficacy, the savings gained by offering only the cheapest could have an adverse economic and social impact on patients personally as well as their ability to contribute as taxpayers. Different people tolerate different treatments differently. There is a real risk with this that someone not tolerating extavia will be left without an alternative. As well as having potentially devastating consequences for the individual and their family, this will almost inevitably lead to extra costs for the taxpayer in terms of medication to manage symptoms such as pain and social and healthcare costs as a result of disability.	Thank you for your comments. The standard process and length of consultation was followed as outlined in NICE's guide to the processes of technology appraisal 2014, relevant for this appraisal. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee was aware that some treatments were associated with a higher risk of specific adverse

			After diagnosis I engaged with other people with MS for support and almost everyone I've met has switched treatments at some point either as a step up or simply because they couldn't tolerate the side effects of the treatment they were on. I have one friend who started on one of the interferons about seven years ago. He couldn't cope with the sickness this caused as a side effect, came off it after a few weeks and decided that the experience was bad that he wouldn't try anything else. That was his choice but, without an alternative, people trying extavia who have a bad experience will be left in the same position without anything unless they presumably quality for one of the stronger treatments (a route I personally wouldn't want to go down unless I believed it was the bast thing clinically because my MS was getting much worse). My friend has problems with mobility, fatigue and is now blind. Of course that may have happened anyway. There is still a direct cost to the NHS because he takes medication to help with pain and mobility. In addition, alternatives will be available to people who can afford it so this decision will only impact on people who can't afford to pay for their medication privately. One size doesn't fit all and there is a real risk this decision will leave many people with MS without treatment at all.	events. The committee saw no evidence suggesting that any treatment had a significantly higher rate of adverse events. Please see section 3.10 of the final appraisal determination.
106	Public	NHS Professional	Glatiramer may well become cost-effective once the generic version becomes available, which has been shown to have similar efficacy to the Teva product. Teva have been trying to block its use. It would be a shame if this was not addressed in this document as if generic glatiramer becomes available this recommendation will immediately become obsolete. I think comparing IFN and glat with best medical Rx and not newer 1st line drugs with same indication (dimethyl fumarate, teriflunomide) makes this guideline much less useful clinically and has generated an odd recommendation. All the 1st line drugs have similar efficacy but the newer oral agents are much more expensive (without any discount) than any of the existing IFNs and glat. It seems paradoxical therefore, that both the newer oral agents are approved for use and yet only Extavia of the older drugs will be recommended. Moreover, the older injectables have a much longer safety record (including during pregnancy for some) and do not carry the risk of PML so some pts who fail Extavia (eg for side-effects) may wish to try another interferon or glatiramer before thinking of using a newer oral agent. This would probably be a more cost-effective approach. So it is counter-intuitive that this NICE recommendation will prevent clinicians offering that option.	Thank you for your comments. Several treatment options are now recommended, including glatiramer acetate. The committee was aware that a generic version of glatiramer acetate is available to the NHS. Please see sections 1.1–1.3 of the final appraisal determination.
107	Public	NHS Professional	This recommendation will imply that we do not have any treatment that can be used in pregnancy. The contraindication against the use of Copaxone in pregnancy has been removed from the updated SmPC. Copaxone is the only medication which is NOT contraindicated in pregnancy. It is true that the SmPC states that it it preferable to avoid Copaxone in pregnancy but it adds "unless the benefit to the mother outweighs the risk to the	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is

			foetus". There are many individual cases where this happens. So what does a woman with active multiple sclerosis who is pregnant supposed to do if she cannot use Copaxone? The revised McDonald criteria for the diagnosis of MS have been published. The definition of clinically isolated syndrome has not changed and this condition has not ceased to exist. Clinically isolated syndrome represents (in most cases) an early stage of MS which one relapse is seen. CIS requires treatment, however treatments that are licensed for people with MS and two relapses in the previous two years are not indicated. Therefore, if a patient has MS but one relapse and active MRI scan what is he/she supposed to do? Extavia preparation means an injection every other day. Injections are associated with flu-like symptoms, and reactions at the site of injections. The appraisal consultation document does not consider that having side effects every other day is different from having side effect once every two weeks (Plegridy), once a week (Avonex) and even three times a week (Rebif). This recommendation will imply that patients cannot choose the medications which give less frequent post-injection reactions. None of my patients (20 years of practice in the MS service) has ever chosen Extavia. When the fever after the injections is high and the side effects are serious, patients do not go to work, and this is a loss of productivity and additional costs to the society. It seems that these costs are not considered in the cost-effectiveness calculation. The following statement in section 3.4: "A single demyelinating event is known as clinically isolated syndrome (CIS), and people experiencing this have a high chance of developing multiple sclerosis" is incorrect, as patients with CIS may have already MS if they fulfil the McDonald criteria for MS (Thompson AJ, The Lancet of Neurology 2017). This should be corrected. The appraisal recognises that some drugs cause more side effects than others, but then it comments on "the size of the confidence intervals", thereby dismissing the significance of the findings. On a personal and societal level, less severe and less frequent side effect are associated with better quality of life, longer time spent in employment and education, which, in turn, it is expected to reduce the indirect costs of MS. The consultation documents concludes that glatiramer acetate, Avonex, Betaferon, Plegridy and Rebif were not cost effective at current prices.	important to people with MS. Several treatment options, including copaxone, are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. Productivity costs are outside the scope of the technology appraisal methods. Please see section 5.5.12 of the NICE guide to the methods of technology appraisal 2013. The committee was unable to make recommendation for treating clinically isolated syndrome because the diagnostic criteria for multiple sclerosis and clinically isolated syndrome has changed. The committee's conclusions on clinically isolated syndrome are available in section 3.4–3.5 of the final appraisal determination. The committee was aware that the frequency of treatment administration may have an effect on adherence to treatment and took this into account. Please see section 3.3 of the final appraisal determination.

			Is it possible to negotiate a lower price for these drugs rather than stopping patients to go on them? I agree that these technologies are not considered innovative anymore, but patients continue to choose them. This is because there are very long-term data (more than 20 years) about these drugs which are substantially safe. All new technologies, which are more innovative, carry much higher risks of serious side effects and their long-term safety data are unknown.	The committee was aware that some treatments were associated with a higher risk of specific adverse events. The committee saw no evidence to suggest that the risk of stopping treatment because of adverse events was different between treatments. Please see section 3.10 of the final appraisal determination.
108	Public	Patient	I have just been made aware of the current consultation taking place on the use of Interferon treatments. I am not sure whether you are taking comments from members of the public and I have been unable to find a designated response site. However I feel it most important to report my views and would therefore be grateful if this e-mail could be forwarded to the appropriate team. I have had MS since 2001 and commenced on Rebif some years later. As you can imagine starting on thrice weekly injections is a very daunting prospect and even now I find it very difficult. However I have no doubt that the medication has delayed the deterioration of my symptoms preventing further reliance on medical and social care. It also enabled me to continue working for the NHS full time as a Health Visitor until I retired four years ago (not for health reasons). I appreciate that the NHS has serious financial considerations which need to be addressed but denying other patients the opportunity to be prescribed this proven medication is very concerning. There is very little available for MS patients. I understand that the recommendation includes that the prescribing of Rebif can be continued until a mutual agreement between Consultant and patient is reached. My concern is that pressure will be put on Consultants to stop the use of Rebif even for existing patients. Life with MS is one of total uncertainty but the use of disease modifying therapies helps a little to continue with as normal life as possible. I am therefore opposed to reducing the choice of therapies available.	Thank you for your comments. The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. These recommendations are not intended to affect people having treatment that was started in the NHS before the guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them until they and their NHS clinician consider it appropriate to stop. Please see section 1.5

				of the final appraisal determination.
109	Public	NHS professional	I am concerned that the only evidence which has been considered is efficacy and cost, and that no evidence has been reviewed regarding side-effects, tolerability or safety in pregnancy. I am concerned that no evidence has been reviewed regarding the pharmacological and clinical differences between the beta interferons and glatiramer acetate. Although the efficacy of the beta interferons and glatiramer acetate are similar, they are completely different classes of drugs with different modes of action and contraindications. For example, beta interferons, including Extavia, are contraindicated in patients with severe depression, but glatiramer acetate is not contraindicated. Depression is common in multiple sclerosis, and so this recommendation means that patients with severe depression will not have the option to be treated with a safe injectable therapy. I am concerned that no evidence has been reviewed regarding differences in side-effects between the beta interferons and glatiramer acetate. For example, beta interferons commonly cause liver enzyme rises, or more serious hepatotoxicity, but glatiramer acetate does not cause significant hepatotoxicity. It is quite common that a patient has to stop beta interferon due to a liver enzyme rise, and for the patient to be then switched to glatiramer acetate. Beta interferons are also contraindicated in patients with significant liver disease, and so glatiramer acetate is the only safe injectable therapy for these patients. I am concerned that no evidence has been reviewed regarding the frequency of administration, and associated tolerability of the different preparations of beta interferon and glatiramer acetate. Extavia is administered subcutaneously on alternate days. There are many patients who find injections very difficult to tolerate, either physically or psychologically, and are unable to adhere to such a frequent administration regime. In these patients, a once a week (Avonex) or once a fortnight (Plegridy) injection is much easier to tolerate and improves adherence (and so efficacy). Beta interferons may also frequently cause post-dose flu-like reactions, which may impair function or be disabling, in which case a less frequently administered preparation is better tolerated. For example, it is common scenario that a patient who is working who suffers flu-like reactions may just choose to inject once a week at the weekend so that the flu-like reaction does not interfere with work. I am concerned that the evidence regarding the safety of the different drugs in pregnancy has not been adequately reviewed. There has been sufficient data to indicate no malformative or feto/neonatal toxicity of Copaxone for the marketing authorisation to be changed so that it is no longer contraindicated in pregnancy. This has resulted in many women choosing to take Copaxone while trying to conceive and, if the risks are felt to outweigh the benefits, to even continue on treatment during pregnancy. As it may take up to several months or years to conceive, if women do not have the option of taking Copaxone, they are at increased risk of	The committee was aware that having a wide range of first-line treatments is important to people with MS. Several treatment options, including glatiramer acetate, are now recommended. Please see sections 1.1–1.3 of the final appraisal determination. The committee was aware that some treatments were associated with a higher risk of specific adverse events. The committee saw no evidence suggesting that any treatment had a significantly higher rate of adverse events. Please see section 3.10 of the final appraisal determination. The committee considered evidence submissions from professional bodies and heard from clinical experts during committee meetings. Please see the committee papers.

			relapse and disability while not on treatment. This recommendation has not reviewed this evidence, but has just considered one part of the sentence in the marketing authorisation which says “it is preferable to avoid the use of Copaxone during pregnancy” but ignores the part of the sentence which says “unless the benefit to the mother outweighs the risk to the foetus”, which may be felt to be the case, and that this is just a “precautionary measure”. Extavia is contraindicated in pregnancy and so, unless this recommendation is implying that Extavia should be prescribed outside the marketing authorisation, this means that women who are trying to conceive cannot be treated and are put at greater risk of relapse. The available data on Extavia in pregnancy indicates that there may be an increased risk of spontaneous abortion, and so most women would choose to stop Extavia before trying to conceive. The recommendation that Extavia is the only option is discriminatory against women. I am concerned that this recommendation which concerns the clinical welfare of people with multiple sclerosis was made by a committee which did not include a single member who has clinical experience of treating multiple sclerosis, such as a neurologist, MS nurse specialist or MS pharmacist. I am concerned that this recommendation is inequitable and does not take into account individual differences in the tolerability or safety of these drugs and is discriminatory against people with multiple sclerosis.	

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

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments end of 24 January 2018

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Biogen Idec Ltd**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**N/A**]
Name of commentator person completing form:	[redacted]

Please return via NICE Docs

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

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments end of 24 January 2018

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

1	Biogen is disappointed by the current decision to only recommend Extavia (interferon beta 1b) as an option for treating multiple sclerosis. Copaxone, Avonex and Rebif, Betaferon and Plegridy have not been recommended based on cost-effectiveness grounds based on pooling of the risk sharing scheme data and lack of consideration for patient and clinician preferences e.g. injection frequencies, routes of administration and incidences of neutralising antibodies.
	
	As stated throughout the process we disagree with the committee's preferred methodology and assumptions. In our view, the approach is unjustified given the evidence available, in particular in the handling of Plegridy.
	
	In the first assessment group report, it was concluded that Plegridy, at list price, was the most cost-effective treatment, dominating (i.e. more effective and less costly) or extendedly dominating all other treatments when treatment specific efficacy and safety were considered. This current recommendation is a stark contrast to the original report where Plegridy is not considered cost-effective.
	
	Plegridy is classified as a new chemical entity and was not included in the risk sharing scheme and unlike Extavia does not have an equivalent product (e.g. betaferon) that did participate in the scheme. It is therefore not plausible to evaluate Plegridy through the pooled data derived from this source.
	
	There is a large body of evidence to support the high clinical efficacy of Plegridy in patients with relapsing remitting multiple sclerosis. Moreover, the design of the pivotal clinical study ADVANCE (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.
	
	ADVANCE is a modern era study in a patient population most likely to receive beta-interferons and glatiramer acetate in UK clinical practice. A total of 2,000 patient-years of experience were accumulated in the study which demonstrated:
	
	• Plegridy significantly reduced the frequency and risk of MS relapses over 1 year, compared with placebo
	  o Plegridy significantly reduced annualised relapse rate by 35.6% at 1 year, compared with placebo (0.256 vs 0.397, p=0.0007).
	  o Proportion of patients relapsed at 1 year was significantly reduced by Plegridy, by 39% compared with placebo (90 vs 142, p=0.0003).
	• Plegridy significantly reduced the risk of sustained disability progression, compared with placebo
	  o Plegridy significantly reduced the proportion of patients with disability progression sustained for 3 months by 38% over 1 year, compared with placebo (0.058 vs 0.105, p=0.0383).
	  o Plegridy significantly reduced the proportion of patients with disability progression sustained for 6 months by 54% over 1 year in a post-hoc analysis, compared with placebo (0.040 vs 0.084, p=0.0069).
	• Plegridy significantly reduced inflammatory disease activity as measured by MRI at year 1, compared with placebo
	  o 67% fewer new or newly enlarging T2 lesions (3.6 vs 10.9, p<0.0001).

	o 86% fewer gadolinium enhancing (Gd+) lesions (0.2 vs 1.4, p<0.0001). o 53% fewer T1 lesions (1.8 vs 3.8, p<0.0001). At the conclusion of the 2-year ADVANCE study, patients were eligible to enter an extension study (ATTAIN). As per the Summary of Product Characteristics (SmPC), 658 patients have completed 4 years in this study programme. Patients receiving continuous Plegridy since Year 1 of the ADVANCE trial (N=376) continued to show low adjusted ARR into Year 6 (0.055–0.203) and low mean number of MRI lesions (new T1 [0.7–0.8], new/newly enlarging T2 [1.9–2.0], Gd+ [0.2–0.3]) up to Year 4. Sustained disability progression confirmed over 6 months also remained low in patients receiving continuous Plegridy, with only 14% of patients experiencing progression at Year 6. This is often a key indicator of efficacy for clinicians and further supports the value that Plegridy offers to patients with MS. The above long-term data has been presented in our original manufacturer submission and in responses to prior consultation but has not been considered by the committee due to lack of apparent statistically significant differences observed in the meta-analysis which is driven by the underlying heterogeneous clinical trials. Therefore, under the current recommendation, an unpublished observational study, which Plegridy did not participate in has been used instead of using Plegridy's own pivotal studies. We disagree with this approach and believe decision making for Plegridy should be based on its own data. Comparing or combining robust randomised controlled trial data with the risk sharing scheme data may be methodologically difficult, however this does not justify the current approach. **We are happy to work with NICE to determine a more suitable methodology where both sets of data can be incorporated and are exploring this independently.** It should be acknowledged there is also an ongoing technology appraisal for relapsing remitting multiple sclerosis (e.g. Ocrevus [ocrelizumab]) outside of the current MTA for which NICE should be seeking to implement consistent methodology (i.e. use of risk sharing scheme data combined with randomised controlled trials). **Both Plegridy and Ocrevus are new chemical entities and should be treated similarly.**
2	Use of the pooled risk sharing scheme effectiveness data in comparison to individual treatment data underpins the perceived lack of cost-effectiveness for the beta interferons and Copaxone not being recommended as part of this ACD. The risk sharing scheme data lacks transparency, is currently unpublished and observational in nature, falling lower in hierarchies of evidence than gold standard randomised controlled trials and meta-analysis. There are several recommendations for assuming class effect within the literature, most with stricter criteria than NICE, however we believe the more lenient NICE criteria used in this MTA were not even met in the risk sharing scheme which was used to inform the economic model of this appraisal. Assumptions of class effect should not be based on efficacy alone, but should also be based on safety. Head to head evidence should be provided to support any assumptions. The supporting evidence for safety was lacking and limited to 'discontinuations due to adverse events' alone. Severe adverse events, adverse events quality of life, were not considered and therefore an assumption of class effect cannot be considered robust. There was direct evidence presented in the assessment report that illustrated evidence of significant differences in treatment effects for different products under consideration (and different regimens of drugs) as presented in prior consultation responses, this is at direct odds with an assumption of a class effect. As previously mentioned, the risk sharing scheme was never designed to assess a class effect but to only ascertain cost-effectiveness of an agent against itself. The risk sharing scheme was always going to show non-inferiority (no statistical significance) when comparing products due to heterogeneity; as confirmed with the wide confidence intervals. Biogen appreciate the complexity and understand the rational for using the risk sharing scheme data as it would be relevant to the UK population, however its use should be only restricted to the agents

	included within the RSS, namely Avonex, Rebif, Copaxone, Betaferon. Using this data to assess the cost-effectiveness of Plegridy is adding further uncertainly to a model that already possess high levels of uncertainty. In contrast, data from matched, adjusted indirect comparison studies have shown Plegridy to demonstrate better clinical outcomes when compared to interferon beta-1a (Rebif and Avonex): ▪ Coyle PK et al. presented results (poster) at the America Academy of Neurology 2017 of a matching-adjusted indirect comparison utilising four Phase III trials of Rebif versus Plegridy. The results at 2 years showed that the proportion of patients with disability progression confirmed at 6 months was statistically significantly lower in the Plegridy group compared to Rebif (6.5% versus 13.2%; p = 0.0007). There was also a lower annualised relapse rate (RR = 0.76, ns). ▪ Scott T et al. presented the results (poster) at the American Academy of Neurology 2017 of a matching-adjusted indirect comparison of clinical effectiveness comparing Plegridy versus Avonex. The results at 2 years showed a statistically significant lower proportion of patients with confirmed disability progression and annualised relapse rates with Plegridy. **The above two studies suggest that Plegridy is different to the other beta-interferons when trial population baseline characteristics are matched, and should be treated on its own as opposed to integration with the RSS data and class effect.**
3	Beta-interferons and glatiramer acetate are grouped together as a single treatment class within this appraisal and therefore may incorrectly be considered interchangeable with no differences in their clinical profile. However, there are important differences between these treatments which may provide patient-level and economic benefits. This is particularly relevant when the heterogeneity of both MS and patient preferences are considered, as these differences can make certain treatments more appropriate for individual patients and therefore impact adherence (as also demonstrated by the differing baseline characteristics and the propensity to be treated with a particular treatment within the risk sharing scheme). In this appraisal, little consideration has been given to differentiating factors beyond efficacy between the beta-interferons and glatiramer acetate due to the current pooling assumptions. Apart from the efficacy advantages already highlighted in this document, Plegridy has additional differences that are of value to patients, for example: • Plegridy is available in a single use, disposable auto-injector which requires no reconstitution, assembly, or disassembly, has the shortest injection time of any IFNβ device (5 seconds vs 10 seconds), and has a needle cover lock to assist in avoiding needlestick injury. • No cold chain storage is required for up to 30 days in comparison to other beta-interferons up to 25 degrees Celsius. This allows flexibility for patients when travelling, not having the hassle of needing to keep their therapy in cold chain; and if travelling for less than 2 weeks, would not require travel with their drug. • Plegridy has the lowest administration frequency per year (26 injections/year), followed by Avonex (52), Rebif (156), Copaxone 40 mg (146), Betaferon/Extavia (183) and Copaxone 20mg (365). Lower administration frequencies are linked to improved adherence, which has been shown to result in improved clinical outcomes and lower disease management costs (Devonshire et al, 2011; Menzin et al 2013; Ivanova et al, 2012; Steinberg et al, 2010; Tan et al, 2011; Treadaway et al 2009). **If the above factors were not considered important by clinicians and patients alike, we would expect to see greater parity in uptake between the beta-interferons and glatiramer acetate in clinical practice, which is not the case**.

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

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments end of 24 January 2018

4	Beta-interferons and glatiramer acetate have been a mainstay of treatment for relapsing remitting multiple sclerosis since their introduction; however, patients may develop neutralising antibodies (NAbs) against beta-interferons which can reduce the efficacy of treatment and have been postulated in prior NICE appraisals to be directly linked to treatment waning. The reported incidence of NAbs in patients with MS varies between <1% and 42%, depending on the beta-interferons tested. Glatiramer acetate is not associated with NAbs. Data from a study by Grossberg et al (2011) show that Avonex has the lowest incidence of NAbs (5-8%) of any beta-interferon; while Plegridy was not available at the time of this study, a study by White et al and the summary of product characteristics (SPC) indicates that NAbs are even less likely with this product (data from patients treated up to 2 years with Plegridy suggests that less than 1% developed persistent NAbs to the interferon beta-1a portion of peginterferon beta-1a). Current waning assumptions applied in the economic model are arbitrary (50%) and in this particular instance where the year 10 implied hazard ratio is used, is overestimating waning when compared to assumptions used in more recent technology appraisal e.g. TA320 (alemtuzumab) and TA 441 (daclizumab) where step changes are applied to 2-3-year data. **We request that the assessment group run further analyses on the risk sharing scheme data to identify the degree of waning specific to each treatment given these reported incidences.**
5	We believe the parity assumption of a 5% annual discontinuation rate (seemingly derived from empirical evidence from the risk sharing scheme) is not applicable to Plegridy which was not included in the scheme and is in contrast to both ADVANCE and ATTAIN. **We request the assessment group and committee provide justification for this assumption given the contrasting evidence available from randomised controlled trials for Plegridy. We also request the assessment group considered year by year data from the scheme to populate the economic model which has the flexibility to consider year 1, year 2 and year 3+ data.**
6	Clarification on page 9, section 3.1. It is stated that "The scheme was set up so that if the drugs were less effective than anticipated, the price would fall", we suggest for transparency, text is also included also stating the counter i.e. "if drugs were more effective than anticipated, the price would increase". The latter occurred for one of the included products during the scheme. Up to year 10 none of the included products performed worse than anticipated and there were no price decreases as a result.
7	Factual inaccuracy: page 6 Plegridy (interferon beta 1b) should be Plegridy (pegylated interferon beta 1a); similarly, Extavia (pegylated interferon beta 1a) should be Extavia (interferon beta 1b)
8	In accompaniment to the above proforma response, we have also submitted a supplementary appendix containing cost-effectiveness results using recently submitted confidential PAS proposals for both Avonex and Plegridy.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted,

please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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

Biogen Idec – ACD supplementary appendix [CIC]

In supplement to the company proforma response, this confidential appendix outlines the impact of Biogen's proposed patient access schemes (PAS) for SC pegylated IFN β-1a 125 µg (Plegridy) and IM IFN β-1a 30 µg (Avonex) on incremental cost-effectiveness ratios. These PAS proposals are contingent on both Plegridy and Avonex receiving positive recommended in the updated guidance for the review of TA32.

The economic model used for the following analyses is fully aligned with AG addendum 7 model release and committee's preferred assumptions. As stated in our proforma response document, we disagree with current committee preferred assumptions which are in part inconsistent with prior appraisals. Biogen have presented results for the present status whilst considering alternative scenarios to meaningfully evaluate cost effectiveness. Additional scenario analyses are documented below with results provided using list prices and confidential net prices.

IM IFN β-1a 30 µg (Avonex)

Biogen have submitted a confidential simple discount fixed price scheme to PASLU for Avonex to the magnitude of [redacted]% altering the unit cost from £163.50 per pre-filled pen containing 30 micrograms to £[redacted].

Scenario analyses:

1. Base case (committee preferred assumptions)
2. Base case with no additional waning at year 10+
3. Base case with pooled HR excluding data after patients switch to any other DMT (variant c1b, slide 14, AC meeting 3)
4. Individual RSS CDP HR for IM IFN β-1a 30 µg
5. Meta-analysis pooled CDP HR + waning aligned with more recent TAs (i.e. 25% at year 2+, 50% at year 5+)
6. Meta-analysis individual treatment effect (ARR, CDP6M) + waning aligned with more recent TAs + Avonex specific annual discontinuation rate (9.9%)
7. Meta-analysis individual treatment effect (ARR, CDP3M) + waning aligned with more recent TAs + Avonex specific annual discontinuation rate (9.9%)

Table 1. List price scenario analyses for IM IFN β-1a 30 µg (Avonex)

Scenario #	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY gained)
1	[redacted]	[redacted]	60,071
2	[redacted]	[redacted]	50,143
3	[redacted]	[redacted]	52,295
4	[redacted]	[redacted]	49,644
5	[redacted]	[redacted]	49,019
6	[redacted]	[redacted]	43,282
7	[redacted]	[redacted]	61,876

Table 2. Net price scenario analyses for IM IFN β-1a 30 µg (Avonex)

Scenario #	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY gained)
1	[redacted]	[redacted]	39,399
2	[redacted]	[redacted]	32,113
3	[redacted]	[redacted]	33,736
4	[redacted]	[redacted]	31,805
5	[redacted]	[redacted]	30,997
6	[redacted]	[redacted]	27,560
7	[redacted]	[redacted]	35,499

Using the committee's preferred assumptions (scenario #1, Table 1) is arguably a worse-case estimate of cost-effectiveness for Avonex where data from all beta-interferons and glatiramer acetate are pooled using the risk sharing scheme data, an unpublished observational study never designed for use as currently implemented in this current ACD. Using the proposed PAS scheme for Avonex and individual (as opposed to pooled) treatment effect data from the risk sharing scheme aligned with its original design, the resulting ICER is close to acceptable willingness to pay thresholds considered by NICE (scenario 4, Table 2). This is further supported by the meta-analysis results with waning applied in a manner more consistent with recent technology appraisal (e.g. TA320, alemtuzumab and TA441, daclizumab). Where disability progression confirmed at 3 months is used (considered less robust or not indicative of permanent progression), the ICER falls marginally above the £30,000 per QALY gained threshold (scenario #7). Where disability progression data confirmed at 6 months is used (as preferred by the EMA and NICE where all treatment comparisons are possible), the ICER falls below acceptable thresholds. **On balance, Biogen believe Avonex represents a cost-effective treatment options for the treatment of relapsing remitting multiple sclerosis with this proposed PAS discount.**

SC pegylated IFN β-1a 125 µg (Plegridy)

In addition to the concerns expressed above with Avonex, Biogen dispute the use of the RSS data to evaluate the cost-effectiveness of Plegridy when it was not part of the observational study. Biogen have presented current committee preferred assumptions whilst considering alternative scenarios to meaningfully evaluate cost effectiveness. These scenarios further support Biogen's concern regarding the uncertainty of using the RSS data exclusively. Additional scenario analyses are documented below with results provided using list prices and confidential net prices.

Biogen have submitted a confidential simple discount fixed price scheme to PASLU for Plegridy to the magnitude of [redacted]% altering the unit cost from £327 per pre-filled pen containing 125 micrograms to £[redacted].

Scenario analyses:

1. Base case (committee preferred assumptions)
2. Base case with no additional waning at year 10+
3. Base case with pooled HR excluding data after patients switch to any other DMT (variant c1b, slide 14, AC meeting 3)
4. N/A – Plegridy not included in the RSS
5. Meta-analysis pooled CDP HR + waning (25% at year 2+, 50% at year 5+) aligned with more recent TAs
6. Meta-analysis individual treatment effect (ARR, CDP6M) + waning aligned with more recent TAs+ Plegridy specific annual discontinuation rate (10.4%)
7. Meta-analysis individual treatment effect (ARR, CDP3M) + waning aligned with more recent TAs + Plegridy specific annual discontinuation rate (10.4%)

Table 3. List price scenario analyses for SC pegylated IFN β-1a 125 µg (Plegridy)

Scenario #	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY gained)
1	[redacted]	[redacted]	60,071
2	[redacted]	[redacted]	50,143
3	[redacted]	[redacted]	52,295
4	-	-	-
5	[redacted]	[redacted]	49,019
6	[redacted]	[redacted]	17,257
7	[redacted]	[redacted]	30,543

Table 4. Net price scenario analyses for SC pegylated IFN β-1a 125 µg (Plegridy)

Scenario #	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY gained)
1	[redacted]	[redacted]	51,802
2	[redacted]	[redacted]	42,931
3	[redacted]	[redacted]	44,871
4	-	-	-
5	[redacted]	[redacted]	41,810
6	[redacted]	[redacted]	13,653
7	[redacted]	[redacted]	25,464

Conclusion

Biogen believe the scenarios 1-3 are inappropriate in the context of Plegridy as they do not consider any of its specific clinical or safety data but are presented for completeness given the current ACD recommendation. Similarly, scenario 5 is based on pooled outcomes which we don't believe is justified in the present case. Plegridy, in the first assessment group report was considered the most cost-effective disease modifying therapy (DMTs), showing cost-effectiveness versus best supportive care and dominance or extended dominance at list price over all other DMTs considered in this appraisal. As such, no discount would have been required. However, the present situation in this ACD is a stark contrast, where Plegridy is no longer considered cost-effective following a change in assumptions, namely the decision to use pool risk sharing scheme data for which Plegridy was not part and deviating from assumptions from previous TAs. **Biogen strongly believe Plegridy should be considered utilising the robust data from randomised controlled trials and meta- analysis (aligned with NICE reference case preferences)**. **At the proposed PAS discount, utilising this robust data consistent with previous NICE appraisals, Plegridy demonstrates cost-effectiveness using 3 or 6 month confirmed disability progression (scenario 7 and 6, respectively, Table 4).**

Please note: these PAS proposals depend on both Plegridy and Avonex receiving a positive recommendation by NICE.

NICE Committee B, Dr Meindert Boysen, Jeremy Powell

National Institute for Health and Care Excellence
1st Floor, 10 Spring Gardens
London, SW1A 2BU

24 January 2018

Dear Committee B, Meindert and Jeremy

Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]: Merck Response to Appraisal Consultation Document

We are surprised and disappointed with the NICE Committee's preliminary decision in the MTA of the interferons and GA for MS, following protracted deliberations during 2017. In Merck's view, the outcome is incompatible with the case that has been presented for Rebif (both in this MTA and indeed in the Risk Sharing Scheme itself) and, even more importantly, the resulting recommendation is unsuitable for MS patients, their physicians and indeed for the NHS.

1. **Rebif is a well established, well tolerated, efficacious and cost-effective treatment option for UK MS patients**

   The Risk Sharing Scheme itself concluded at its end that the drugs in the scheme, including Rebif, were cost-effective (based on the RSS parameters). In this subsequent NICE appraisal, real world evidence of Rebif's value has been described following more than 15 years of use of the drug by NHS patients. Additionally, Merck further reduced the Rebif price to satisfy the context in which the cost-effectiveness question is now being revisited.

   Our conclusion on the cost-effectiveness of Rebif differs from the Committee's for two main reasons:

   a. In our modelling we utilise Rebif's own efficacy result from the Risk Sharing Scheme whilst the Committee instead have pooled the results of the individual RSS products. We continue to defend our position that this pooling is an inappropriate use of the RSS data. We have outlined our rationale for this previously in several documents (the original Merck submission, our response to the TAG, the resubmission in September 2017). The RSS was set up to compare individual products versus standard of care, not versus the other products (implicit in using the data in the way the Committee propose). As well as being

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unsound for academic reasons, this approach is prejudicial against the more effective products which will bear a disproportionally higher price impact than would be borne if they were assessed using their individual RSS result.

b. The Committee have chosen to follow the TAG's approach to mortality modelling rather than an alternative method which has been accepted previously by NICE in other MS submissions (TA254, TA303, TA312 and TA441). Merck provided the functionality in the TAG model in order that this alternative method could be applied to all drugs in this appraisal. We are with the Committee in acknowledging the uncertainty in modelling of this parameter, but we aren't satisfied that the Committee's conclusion about the Pokorski method is reasonable. Should its use in prior decision making be revisited?

2. The current draft recommendation is unsuitable for UK MS patients and their physicians as it restricts patient choice to a single treatment (of the six that were included in this MTA). The decision significantly limits UK patient choice and raises several fairness and equity points:

- We question whether the demands for platform DMDs of 5000 new MS patients each year – who currently have the option of all six DMDs in this MTA – can be met by a single medicine. Extavia currently has <1% market share[2]; if physicians continue to elect alternative treatment options for new patients, those which we believe to be more expensive treatments – such as Tecfidera, Aubagio and Lemtrada may be preferred; in such a situation, the NHS is unlikely see any cost savings as a result of this recommendation;
- By assuming that the efficacy of the non-RSS medicines is that which has been established for Avonex, Betaferon, Copaxone and Rebif via the Risk Sharing Scheme, the non-RSS medicines have not been subject to the same level of scrutiny of and challenge to long-term effectiveness as the RSS products; instead they've been allowed to 'borrow' the certainty established through considerable investment by other companies and stakeholders. As a participating company in the RSS, this appears unfair to Merck. The RSS was effectively an observational study which ran from 2002 to 2016 and aside from providing access to DMDs to thousands of patients with MS and evidence on the long-term effectiveness of the participating treatments, it has also been credited with supporting the development of the MS treatment infrastructure

[2] Based upon data from IQVIA's hospital market survey tracker, a service which surveys a panel of MS physicians each month providing insight into product market shares and prescribing behaviour.

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in the UK, in part thanks to the participating companies' contributions to service development;

- Above we've summarised our objection to the pooling of the RSS efficacy results, but there is a related point; in assuming that the RSS efficacy results show that DMDs 'work similarly', can be pooled and can therefore be applied directly to Extavia (and other drugs) in the economic model, the Committee are also implicitly assuming that the drugs have comparable *utility* for patients and physicians and a comparable safety profile. This doesn't seem reasonable in light of different drug delivery mechanisms for patients and the significant variation in levels of patient support that are available through company sponsored programmes. 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. This is complemented by RebiSmart®, an electronic injection device developed to help provide easier administration for patients and to track adherence. These distinguishing features of the different treatments are lost in the assumptions in this MTA.

Merck has long shared the ambitions of NICE and the NHS to see continued access to the current complement of treatment options for patients with multiple sclerosis, including Rebif. This has motivated our participation in the Risk Sharing Scheme and continues to motivate our full and active engagement with the NICE process during this appraisal. We stand behind Rebif's current value proposition and - on the basis of applying what we believe to be reasonable modelling assumptions - repeat our previous conclusions that Rebif's ICER versus BSC is below the current willingness to pay threshold for the NHS. We ask the Committee to reconsider their initial decision, in light of these technical considerations and because removing all platform MS treatment alternatives except Extavia is incompatible with the clinical and cost effectiveness evidence and will result in negative consequences for MS patients and their physicians.

Yours sincerely,

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

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments end of 24 January 2018

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Novartis Pharmaceuticals UK Ltd.
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Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]

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Name of commentator person completing form:	[redacted]
Comment number	**Comments**
1	Section 3.2 of the Appraisal Consultation Document (ACD) provides a list of disease-modifying therapies for relapsing-remitting multiple sclerosis (RRMS) that have been appraised by NICE since the original appraisal of beta-interferons and glatiramer acetate. *"Since NICE originally appraised these drugs, it has recommended other treatment options for relapsing–remitting multiple sclerosis including alemtuzumab, cladribine, daclizumab, dimethyl fumarate and teriflunomide."* However, fingolimod (TA254; 2012) and natalizumab (TA127; 2007) are not included in the list, despite having also been appraised by NICE as treatments for RRMS. In these appraisals, fingolimod and natalizumab were recommended by NICE in specific subgroups, highly active and rapidly-evolving severe (RES) RRMS, respectively (as defined in the final guidance issued by NICE). It should be noted that daclizumab and cladribine, which are already included in the list in the ACD, are also recommended for specific subgroups of RRMS (previously-treated, active RRMS or RES RRMS, as defined in the final guidance issued by NICE). For clarity, Novartis requests that the wording of Section 3.2 be changed to include fingolimod and natalizumab to complete the list of treatments for RRMS appraised by NICE as follows (suggested changes marked in red text): *"Since NICE originally appraised these drugs, it has recommended other first-line treatment options for relapsing–remitting multiple sclerosis including alemtuzumab, ~~cladribine, daclizumab,~~ dimethyl fumarate and teriflunomide; in addition, NICE has recommended natalizumab, fingolimod, cladribine and daclizumab in specific subgroups, as defined in each appraisal."*

Insert extra rows as needed

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms

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that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Teva UK Limited** **Ridings Point** **Whistler Drive** **Castleford** **WF10 5HX**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
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NICE National Institute for Health and Care Excellence

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Teva finds that the recommendations within this ACD do not form a sound and suitable base for the NHS as they would restrict access to medications for relapsing-remitting multiple sclerosis. The current availability of Copaxone (glatiramer acetate) and several beta interferons allows for patients and clinicians to choose a treatment that is most suitable for every patient, as occurred while the RSS was in operation. An FAD based on this ACD would prevent any tailoring of therapy and force all patients to have a single treatment irrespective of their specific needs.
2	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, and the resulting conclusion that the RSS data for all four disease modifying treatments (DMTs) could be pooled. Teva has provided reasoning for this position in its submission (dated 29 September 2017). Teva stands by these comments and would like to add that this approach is inconsistent with previous appraisals in multiple sclerosis, where Copaxone and the individual beta interferons have been considered separately; *e.g.* the appraisals of daclizumab, dimethyl fumarate, alemtuzumab, teriflunomide and fingolimod. The Committee has been consistent with previous appraisals across a number of areas (*e.g.* disease state costs and the inclusion of carer's disutilities), but not in the consideration of a class effect between Copaxone and beta interferons. Teva considers this to be both unreasonable and unfair.
3	A brief recap of the points previously raised by Teva now follows, as we feel that these are still relevant and have not been sufficiently considered by the Committee. The Committee gave three reasons for its determination of a class effect: (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. In summary, there is no scientific basis for assuming a class effect between all four DMTs for the following reasons: • 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 pregnancy, 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 previous appraisals of DMTs for multiple sclerosis 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 With specific regard to the NMA: • There is no credible evidence from randomised clinical trials to prove equivalence in efficacy between Copaxone and the beta interferons o 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 o 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 o 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: o 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 of Copaxone o 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 product granted an increase in price following analysis of data
4	Selection bias Teva has undertaken additional analyses in order to address the other points raised by the Committee as justification for pooling. Firstly, the fact that the RSS was potentially subject to selection bias. Teva agrees that there is selection bias in the RSS; however, this provides justification for *not* pooling the individual DMT data, for the following reasons: • Any selectivity in patients was a reflection of normal NHS clinical practice – the specific results for Copaxone reflect its cost-effectiveness in the context of the particular clinical circumstances in which it is used in the NHS in comparison to best supportive care (BSC) (as this is what the RSS was set up to do) • 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 • Furthermore, any evidence of selection bias raises further doubts on the suitability of the recommendations within the ACD, as this would show that 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 has undertaken an analysis of the baseline characteristics of the patients on Copaxone within the RSS and those on beta interferon. The results add evidence that supports the hypothesis that the allocation of patients between Copaxone and beta interferon treatment was non-random. This analysis revealed that there were significant differences in the mean values ($p<0.05$) and the variances ($p<0.01$) for age at symptom onset ([commercial in confidence information removed]), EDSS at baseline ([commercial in confidence information removed]) and years of MS at baseline ([commercial in confidence information removed]) between Copaxone and beta interferon patients. An analysis of gender also revealed differences that were borderline significant (percentage female: [commercial in confidence information removed]; $p=0.051$). Furthermore, the RSS included some patients with secondary progressive multiple sclerosis, which is a population that is not eligible for treatment with Copaxone; this again produces a significant difference between the patient populations (percentage relapsing-remitting multiple sclerosis: [commercial in confidence information removed], respectively; $p<0.001$).
5	Switching Secondly, the fact that patients who switched treatments in the RSS were excluded from the calculation of the hazard ratio (HR) for Copaxone (as well as for the beta interferons). Teva believes that as NICE and the Assessment Group have access to the full data from the RSS, it would be straightforward to complete an analysis that included switches and, thereby, that addressed the concerns of the Committee. Teva has undertaken this analysis for Copaxone and recalculated the HR with all patients included (both switches to other RSS DMTs and to non-Scheme DMTs). This produces a HR of [commercial in confidence information removed]%, which compares to the [commercial in confidence information removed]% previously reported with switches excluded. When this updated value is included in the economic model using all other parameters at the Committee's preferred values, it has the effect of producing an ICER for Copaxone of £[commercial in confidence information removed] *versus* BSC.

	Teva feels that these calculations give the most accurate assessment of the efficacy and cost-effectiveness of Copaxone, taking into consideration the Committee assumptions and preferences. Teva has undertaken a further analysis of the switching that occurred within the RSS using the 6-year data (latest available on which this analysis could be conducted). Kaplan Meier analysis was undertaken with any switch to another DMT set as the event for each analysis and the year of switch since baseline as the time interval. This analysis revealed that the pattern of switching is both qualitatively and quantitatively different between Copaxone and the beta interferons. [commercial in confidence information removed]. These results demonstrate further distinct differences between treatment with Copaxone and the beta interferons and add further argument against the use of pooled RSS data, as outlined in the previous comment.
6	Teva is of the opinion that the RSS should be used for its original purpose: to provide real world evidence of the clinical benefits and cost-effectiveness of the individual RSS DMTs against BSC (with no comparative analysis between DMTs). The data from the RSS represents the most reliable evidence for these treatments when considered individually. Whilst the pooled results give an overview of the Scheme, these results do not reflect the individual efficacy of each DMT. 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. The design of the RSS provides no scientific validity of an assumption of a class effect between the DMTs. 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.
7	Upon further examination of the economic model supplied by NICE, 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. Under the Association of British Neurologists' guidelines at the commencement of the RSS, a cut-off for treatment of EDSS 7 was established (equivalent to patients being non-ambulant).[1] However, at the time of establishment of the RSS there were no other DMTs available and so treatment was often continued, and this was therefore reflected in the model. However, 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. This reality was noted in the ACD where it was stated "*The committee understood that people have treatment until they can no longer walk, when they stop treatment*." Therefore, the inclusion of these costs is questionable and an artefact of the original model and does not reflect current practice, as noted by the Committee. Exclusion of these costs has a small, but meaningful effect on the ICER for Copaxone, producing a value of £[commercial in confidence information removed] compared to £[commercial in confidence information removed] using the Committee's preferred assumptions. (The details of this oversight are as follows: within the sheet labelled 'States', on row 9 drug costs are included for EDSS states 7, 8 and 9.) **Reference** 1. Department of Health. Cost-effective provision of disease modifying therapies for people with multiple sclerosis. HSC 2002/004; 4 February 2002. Available at http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4012214.pdf [Accessed January 2018].
8	Teva is concerned that the beta interferons are referred to by brand name in the ACD, whereas Copaxone is referred to by its International Non-proprietary Name. For consistency and clarity, Teva requests that the brand name 'Copaxone' be used. In addition, a press release on the ACD refers to communication from NICE that states that the guidance covers only branded Copaxone;[1] in which case, the brand name for Copaxone must be used to prevent misinterpretation of the recommendations from this appraisal.

Consultation on the appraisal consultation document – deadline for comments end of 24 January 2018

	Reference 1. https://pharmaphorum.com/news/nhs-funding-five-ms-drugs-threat/ [Accessed January 2018].
9	Pregnancy was considered by the Committee as an equality consideration. However, in the ACD it was stated that, as Copaxone was still recommended to be avoided during pregnancy, no special considerations were necessary. Teva would like to add that it is not just during pregnancy, but also when women with multiple sclerosis are considering starting a family, that Copaxone has an important role in treatment. Copaxone is currently the preferred DMT for multiple sclerosis in women wishing to become pregnant, and it can be used up until pregnancy in all cases, and during pregnancy in cases where the benefits of continued treatment outweigh the risks.[1,2] **Reference** 1. Pregnancy and birth. MS Society, London. Available at https://www.mssociety.org.uk/what-is-ms/womens-health/pregnancy-and-birth [Accessed January 2018]. 2. Copaxone (glatiramer acetate) Summary of Product Characteristics. Teva UK Limited.
10	Teva supports the proposed date for reviewing the guidance of 3 years after publication.
11	Teva has submitted an application through PASLU for a new Patient Access Scheme for Copaxone (both dosing regimens) with a discounted price of £[commercial in confidence information removed] *per* pack (28 days). Teva requests that this is considered by the Committee.
12	With the assumptions outlined above (*i.e.* PAS price for Copaxone, Copaxone-specific RSS data with all patients who switched treatment included, and drug costs removed from EDSS states 7-9) included in the Committee's preferred version of the cost-effectiveness model, produces an ICER of £[commercial in confidence information removed] *per* QALY for Copaxone, demonstrating a strong cost-effectiveness of this treatment.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	MS Society
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
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Example 1	We are concerned that this recommendation may imply that ……..
1	**Summary** We are concerned that the recommendation to restrict the number of treatments used as first line therapies could have a detrimental impact on the lives of people with MS. While we acknowledge that all of the treatments appraised are similarly effective, there are important reasons why people with relapsing MS prefer different beta interferons or glatiramer acetate over Extavia. These include a variety of reasons unrelated to efficacy but nevertheless important in ensuring people start and remain on a treatment. Reasons include mode of delivery and ease of use, side effects, storage requirements, impact on daily life and whether they are planning to start a family. Limiting the range of beta interferons and glatiramer acetate to Extavia only is likely to increase the chances of people choosing not to take any treatment at all and in turn experiencing potentially avoidable relapses and disease progression. Less people managing their MS as well as they would otherwise would will mean a greater burden on wider NHS services and carers. “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 As MS affects everyone differently people find that different treatments are better suited to their MS. Beta interferons and glatiramer acetate have been used for years as the first line treatment when taking an escalation therapy approach to treating MS. The current ABN guidelines state MS specialists may adopt an escalation approach, starting patients on a less toxic drug and only switching if this does not control their disease. Limiting the number of less toxic treatment options will result in more people choosing not to start any treatment. While many people with MS are currently taking beta interferons or glatiramer acetate, Extavia has been one of the least prescribed options within this category.[1] The low prescribing rate of Extavia is likely due to the fact that people with MS generally choose to take one of the other treatments looked at within this appraisal.
2	**Impact on people who’ve experienced single clinical episode** Under these recommended changes, people who have experienced a single clinical episode with multiple MRI lesions (regardless of whether they have had an MS diagnosis or not) will have their treatment options severely limited. These recommendations would mean that people diagnosed with MS who have had only one clinical episode with MRI activity will now only have the option of taking Extavia or alemtuzumab. As acknowledged in the DMT alghorithm, alemtuzumab is unlikely to be prescribed for someone who has only experienced one clinical episode, so in practice people who’ve experienced one relapse will only be eligible for Extavia and will have no option to switch to another beta interferon if they

[1] Redfern-Tofts, D., Wallace, L. and McDougal, A. (2016) My MS, My Needs 2: technical report

	experience negative side effects while taking Extavia. Those people, who would have preferred to take a different beta interferon over Extavia, due to a reason other than its clinical efficacy, will most likely choose to go without treatment. This would mean a delay in starting a treatment until they have another clinical episode and therefore qualify for a greater number of treatments. This would risk their MS progressing faster than it would have if they had a wider range of first line treatment options. This recommendation would unfairly impact on this subgroup of people with MS who would have their options severely limited.
3	**Safety profile of beta interferons and glatiramer acetate** Though less effective than some of the newer treatments now available, beta interferons and glatiramer acetate are an important option for pwMS. They offer people who are less inclined to take risks a treatment option 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. The greater the range of DMTs available means that more people are likely to find the treatment that suits them. If these DMTs were no longer available on the NHS, it could result in less people being effectively treated for their MS. The Association of British Neurologists (ABN) specifically recommends beta interferons and glatiramer acetate for 'individuals with relatively quiescent disease'.[2] 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 by case studies gathered by the MS Society (to inform our previous submission to the MTA); several people commented on feeling most comfortable with the known risks of the more established DMTs opposed to newer, riskier DMTs. 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.[3] 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.
4	**Mode of Delivery** The reasons different people choose to take one treatment over another are diverse and not just related to the clinical efficacy of each treatment. One of the strongest influences on why someone chooses one treatment over another is mode of delivery. When given a choice to take one of the beta interferons or glatiramer acetate, a number of people with MS have told us that the reason they chose their treatment was because it was administered less frequently. People particularly mentioned choosing Avonex because it is administered once a week, and Plegridy because it is administered fortnightly. This means that they spend less time having to think about treatment, less time self-injecting and less time dealing with side effects. As one person who has been taking Avonex for years commented:

[2] 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

[3] Fox et al, Risk tolerance to MS therapies: survey results from the NARCOMS registry, Mult Scler Relat Disord. 4(3):241-9, May 2015

	"In the absence of any other information or reassurances from NICE that the side effects of Extavia do not last anything like as long as those from Avonex, then their recommendation is more or less restricting some future patients to an interferon treatment that leaves them substantially impaired for most of the time." On the other hand, some people with MS who experience cognitive issues have told us they chose a treatment which is taken more frequently as they find it easier to remember and keep to the schedule. This reflects the variation in why people with MS choose different treatments. Another mode of delivery factor that many people with MS have commented on as an influence when choosing a treatment is the pre-filled '*straight forward pen device*' which many are self-administered with, including Rebif, Plegridy and Avonex. These developments in how the DMTs are administered show that improvements are being made to reduce the side effects and ease of use. One factor that dissuades many from choosing Extavia is that it comes in a powder form that the patient has to mix before administering, with a 44 page instruction pack Extavia is clearly not the simplest beta interferon to self-administer.[4] For people who have problems with dexterity or cognitive issues, the complicated process for taking Extavia can be extremely off putting. Without the option of easier to take treatments, many people with MS would likely need more support from a carer to help administer Extavia. 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.
5	**Side effects** The side effects that each beta interferon and glatiramer acetate come with play a big role in influencing why someone opts for one drug over another as well as why many people switch from one to another. Side effects of beta interferons include flu like symptoms which people experience after injecting as well as unpleasant injection site reactions which lead some people to develop needle phobia. A number of people have told us that they chose Copaxone as their treatment option when they were first diagnosed as they were informed it had fewer side effects than the beta interferons. We have also heard from people who are concerned that they will not be allowed to continue with their treatment if, due to issues such as thyroid problems, they are required to take a break. One person commented "taking any of these drugs is stressful enough without having the extra stress of removing what may have been the only drug which worked for my body". Only having the option of Extavia would likely result in many people who experience side effects having little other treatment options. This was the case with one person who told us that they had only been offered Extavia due to their MS nurse telling them it was the cheapest option and that they would only be considered for another option if Extavia proved ineffective. Not given a role in deciding which treatment they would prefer, this person had a negative experience with Extavia due to side effects, commenting: "It made me feel worse, more dizzy etc so only lasted 3 months on it. A neurologist even thought I was suicidal when I said I felt better having nothing than that injection".

[4] https://www.extavia.com/assets/pdf/injection-training-manual.pdf

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

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Consultation on the appraisal consultation document – deadline for comments end of 24 January 2018

6	**Innovation** In paragraph 3.2 the committee highlights that 'its remit was to revisit the original appraisal, and to compare to beta interferons and glatiramer acetate with best supportive care, rather than the newer drugs'. However, in paragraph 3.25 the committee reports that while the treatments may be considered innovative compared with best supportive care, they are not when compared to the newer treatment options and therefore should not be considered innovative. This argument 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.
7	**Copaxone's use during conception and pregnancy** Currently Copaxone is the only licensed treatment for relapsing MS which is not contraindicated for pregnancy and is often chosen by women who are planning to start a family. The argument put forward in the appraisal consultation document that 'special considerations' shouldn't be applied for Copaxone due to the marketing authorisation suggesting that it is preferable to avoid taking during pregnancy ignores the evidence from both people with MS and their clinicians. We have heard from neurologists who have expressed particular concern over this aspect of the recommendation highlighting that they regularly prescribe Copaxone to women who are planning a pregnancy as the risk of not taking a treatment at all outweighs the risks involved in taking Copaxone while pregnant. As it is not contraindicated in pregnancy, the judgement on the risk involved, is down to women with MS and their neurologist, the committee should not be making this judgement on their behalf. NICE should listen to the judgement of neurologists who regularly make decisions with their patients on whether Copaxone is safe to take when pregnant and breastfeeding. Women with MS who are planning a family in the near future have written to us to express their concern over this recommendation. They highlight that they are aware of the risks involved in taking Copaxone while pregnant but that they are more concerned over the risk of going without treatment for a long period: "I am very disheartened to hear that NICE might decide to stop this treatment, as I understand Copaxone is the only medication that is ok to take - although I understand there are risks to any medication taken in pregnancy....with a more severe RRMS, I am quite worried about completely stopping all treatments, especially during the pre-pregnancy bit, and if it takes many months to conceive". We have been contacted by women who plan to switch from treatments such as dimethyl fumarate to Copaxone while they try to start a family. The committee's recommendation that Copaxone does not deserve special consideration goes directly against Copaxone's licence and general prescribing practice in England and Wales and should be reconsidered.
8	**Pharmaceutical company support** The appraisal consultation document makes no mention of the extra support given by some of the pharmaceutical companies to help people take their products. If Extavia is the only option for new patients we would want to see that they are given the same level of support that those who are already taking one of the other beta interferons receive. While Extavia may be the most cost effective option does this factor in the 24 hour nurse support phone number that some of the other treatments provide?
9	**Lifestyle factors** Lifestyle factors for people with MS are often a big reason why they choose one treatment over another. The storage requirements of these different treatments mean that people find one is a better fit around their daily life. For example a cold chain is less essential when taking Plegridy, which makes it a more practical choice for people who need to travel a lot such as people with MS who

	serve in the military. More frequent injections that need to be stored in a refrigerator make it difficult for people to travel. A number of people have commented to us that they simply stopped going abroad while taking beta interferons as they found it too much hassle. Compared to many of the treatments approved more recently by NICE, beta interferons and glatiramer acetate have less burdensome monitoring requirements, with 6 monthly blood tests for the former and none for the latter. This can be a factor in why people choose one of these treatments: "I still work, I cannot afford to be off work with side effects of some of the other medication. I didn't want to have to attend regular blood tests as required for some drugs I had a choice of. I felt that with the minimal effect on my body that this medication would suit me best."
10	**Impact on newer appraisals** We would like to see some consideration over what impact this could have on the appraisals which have taken place since 2002 which have used beta interferons and glatiramer acetate as a comparator. Would newer appraisals have to go to reappraisal? This would cause a great level of concern for people with MS currently on these treatments.
11	**Lack of transparency** We do not feel that the basis for this decision has been transparent. The recommendation of the appraisal consultation document sees all of the treatments as of a similar efficacy, and therefore base's its decision on the cost effectiveness of each option. As cost effective analysis is not provided within the document we are unable to make an argument as to whether more treatments than Extavia are cost effective. The discussions with pharmaceutical companies over the price of their products have also not happened in the public domain and we are unable to scrutinise these decisions. While the risk sharing scheme has been used as the key data for this appraisal, the final results are still yet to be published, this is another reason why the decision to provide Extavia alone is not as transparent as it should be. It is unclear to us why NICE and the Department of Heath have not made this data available to the public and we would like to know why this decision has been made.
12	These recommendations will also unfairly impact on people who: - Have a history of seizures and shouldn't be offered beta interferon but can be offered glatiramer acetate - Are unable to swallow tablets and will have their first line treatment range reduced to Extavia and Alemtuzumab only.
14	We would also like to know how this recommendation would impact people who are currently taking one of the restricted treatments but are required to have a break for some reason. Would they be required to start Extavia instead despite having been taking one of the other options previously?

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more

information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments end of 24 January 2018

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Multiple Sclerosis Trust**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

Please return via NICE Docs

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

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Consultation on the appraisal consultation document – deadline for comments end of 24 January 2018

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Summary** **We strongly believe that all current treatments should remain available as a treatment option for all eligible patients.** • **We consider that the proposal to recommend Extavia alone is discriminatory towards those for whom problems with dexterity, vision and cognition form part of their disability (see 3.1).** • **We consider that the proposal to recommend Extavia alone is discriminatory towards women of childbearing age who intend to conceive, as it will remove all appropriate treatment options (see 3.6).** This decision has been made without reference to clinical practice or experience and ignores significant real-world differences between each of the beta interferons and glatiramer acetate. We are particularly disappointed that this recommendation does not acknowledge individuality and would take away choice from people with MS. NICE has acknowledged that all six drugs are equally effective at reducing the number of relapses and slowing down disability progression. The decision to approve Extavia and not the other five drugs is based on the cost of the drugs; Copaxone and the other beta interferons are more expensive than Extavia. No consideration has been taken of the potential impacts on people with MS and on specialist MS services or the costs of these impacts. The MS Trust's expertise lies in understanding and representing the perspectives of people with MS and ensuring that people have access to effective treatments. We invited comments on the ACD from people affected by MS and from health professionals. Over 500 people with MS and over 100 specialist MS health professionals (26 neurologists, 73 MS specialist nurses, 5 MS specialist therapists, 4 pharmacists) responded to our survey; their feedback has informed our response to the ACD and is provided in the appendices to this document. In both surveys, 98% of respondents disagreed with the NICE recommendations, and many gave explicit examples to explain their response. We urge you to look at our supporting appendices to see what people with MS and specialist MS health professionals have said about the recommendations.
2	**Importance of beta interferons and glatiramer acetate in the current treatment pathway** Because of the unique circumstances of this multiple technology appraisal, the committee is in the position of appraising six drugs which have been prescribed by the NHS for more than fifteen years. The drugs are established treatments with well-defined safety profiles. MS teams are very experienced with these agents; there is a wealth of published research and clinical experience confirming their general safety; there are well-established services to initiate and monitor

	treatment. Despite the availability of alternative oral treatments since 2014, the beta interferons and glatiramer acetate continue to be prescribed widely. Extensive real-world experience of these agents has confirmed that at an individual patient level, different products suit different individuals. There are significant differences between the drugs in terms of ease of use, dosing schedules, storage, side effects, safety during pregnancy and tolerability. These factors impact on different people to a greater or lesser extent, and individuals will have personal preferences which enable them to effectively manage their treatment. 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. Shared decision making is a priority for the NHS and has become an important component of helping patients to choose the disease modifying drug which is right for them. Approving Extavia alone and withdrawing the remaining beta interferons and glatiramer acetate will severely limit the potential for MS teams to share the decision process and find a treatment that is right for the individual and their circumstances. 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[1]; for many people, their MS has remained stable while taking one of these 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; others who have started with one of the oral treatments have experienced side effects and switched to one of the beta interferons or glatiramer acetate. The impact on patient care of approving Extavia alone and withdrawing the remaining beta interferons and glatiramer acetate should not be overlooked. Our comments focus on the following major issues: • impact on people with relapsing MS • impact on MS services • overarching criticisms of the appraisal
3	**Impact on people with relapsing MS** The differences between each of the beta interferons and glatiramer acetate have a significant impact on people with MS, this has not been taken into account by NICE in reaching this decision. In pooling the data from the RSS, which excluded Extavia, the differences between the drugs was not apparent; yet the impact of this real-world difference on patient adherence should not be overlooked. Dosing schedules, storage, side-effects and tolerability vary greatly between the drugs and we have reports of people who have had bad experiences on a particular drug, which leads to non-adherence. Non-adherence on a particular drug because of a bad experience, can also lead to disillusionment with MS treatments in general. Evidence demonstrating the value of treating people with MS early is compelling, and therefore if people refuse treatments this can lead to poorer health outcomes and increased disability, which increase the demand for services and therefore costs to the NHS. Our own research and that of the MS Society shows that Extavia is the least prescribed of the six modifying drugs under consideration[2]. In our HP survey, 11% of respondents commented that all

[1] Scolding N, et al. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. Practical Neurology 2015;15(4):273-279.

[2] MS Trust. Evidence for MS specialists: findings from GEMSS. Letchworth: MS Trust; 2016
MS Society. My MS, My Needs 2016: access to treatment and health care. London: MS Society; 2016

	treatments except Extavia were offered by their MS team; 9% of respondents commented that Extavia was offered as an option but no one on their caseload was taking it. In our survey of people with MS, just 0.4% (2/522) indicated that they had taken Extavia. Particular issues around ease of use, injection frequency and other factors are explored below, demonstrating why this is the least preferred of the options.
3.1	**Ease of use** **We consider that the proposal to recommend Extavia alone is discriminatory towards those for whom problems with dexterity, vision and cognition form part of their disability.** All of the drugs under evaluation, with the exception of Extavia and Betaferon, are provided as ready-to-use injection devices. Extavia is supplied as solvent and powder which must be made up each time it is taken. The Patient Information Leaflet for Extavia **details the seventeen step instructions** for doing this: www.medicines.org.uk/emc/files/pil.6529.pdf. For the MS Decisions resource we prepared a video which shows how the injection is made up https://youtu.be/bxyMMa2vNHA and injected https://www.youtube.com/watch?v=Q0_RopyN66w). People with manual dexterity, visual or cognitive difficulties, all of which are common problems in MS, will find this very difficult, if not impossible, to do. Those with fatigue or busy lives will also struggle to make up and inject Extavia every other day. 13% (70/522) people with MS responding to our survey mentioned ease of use as a major criteria for choosing an injectable disease modifying drug. People with MS: *They should try mixing Extavia with gloves on. Hopefully they will realise how difficult it can be for people with reduced dexterity due to lack of sensation in finger tips.* *Smaller needle albeit three times a week, came already filled, I could and still self-inject especially as I have dexterity issues meant didn't have to faff about and do it myself swiftly and easily. Still the case as I live by myself.* *I take Avonex and chose this drug because you inject with an easy to use pen once a week.* MS specialist: *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.*
3.2	**Injection frequency** The drugs under evaluation are self-injected at different intervals, from daily to once a fortnight. Injection frequency is one of the most important factors in treatment choice, with daily, weekly or fortnightly frequencies being most popular. Extavia is injected every other day, a pattern that is not easily remembered. Over a two week period, patients are injecting on a different day of the week, which increases the risk of simply forgetting to do an injection and consequently losing therapeutic effect. Ultimately, it increases the risk of relapses, of someone discontinuing treatment altogether and in the longer term acquiring greater disability due to relapses or progression.

	More frequent injections lead to a higher incidence of injection site reactions, increasing the need for hospital visits to deal with infected injection sites and increasing the risk of discontinuing treatment. Patients are instructed to rotate injection sites; with less frequent injections, there is more opportunity for an injection site to recover before it is used again. 20% (103/522) people with MS responding to our survey mentioned injection frequency as a major criteria for choosing an injectable disease modifying drug. People with MS: *Only having to manage the injection every two weeks means that any side effects are limited to every other weekend and have not impacted on my ability to work full time.* *I chose Avonex initially as injection was weekly and the least invasive to my life. The same decision I made when swapping to Plegridy which was a fortnightly injection.* *I am considering Plegridy as it is once a fortnight and the side effects appear manageable.* MS specialists: *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.* *People choose the other injectables for a variety of reasons e.g. less frequent injections.* *Extavia has the same efficacy as the other injectables, but is not chosen by people with MS as it is difficult to remember to take it being on alternate days. We now have more people on Plegridy and Copaxone. The former because of the less frequent administration and the latter due to its lack of side effects profile.*
3.3	**Side effects** People often experience flu-like symptoms after each beta interferon injection. These can be severe and are a major reason why people stop taking one of these drugs. Every other day injections required for Extavia make it particularly difficult to manage the impact of flu-like symptoms on work and family life; less frequent dosing schedules such as weekly or fortnightly make it possible to plan injections at a time (for example over the weekend) when flu-like symptoms will have less impact. Glatiramer acetate does not cause flu-like symptoms and is often a preferred option for this reason. Other disease modifying drugs are associated with side effects which are a significant concern for some and influence choices made by neurologists and patients. Dimethyl fumarate carries the risk of a serious brain infection, alemtuzumab leads to thyroid problems and there is an increased risk of birth defects in women taking teriflunomide. Some side effects make drugs unsuitable for people with pre-existing conditions, for example gastrointestinal side effects make dimethyl fumarate unsuitable for people with gastritis or inflammatory bowel syndrome. The severely restricted list of drugs that would be available as a result of this ACD will make it much more difficult for MS specialists and patients to choose a suitable treatment based on side effect profile, either at treatment initiation or, more importantly, treatment switching. People with MS: *Extavia worked fine until I was too bruised and skin hardened so injection liquid started coming out again. Switched to Tecfidera, but am having problems with side effects still after half a year, so don't know what to switch to now.*

	Copaxone, despite having one possible nasty side effect, appealed to me because it would not leave me with flu-like symptoms and needing to take additional medication to combat it. *Based on thinking through options available chose Copaxone as it did not cause flu symptoms on injection days.* *I felt flu like side effects during the night of administration, and sometimes the next day, which is frustrating, but it is ok as it is only one day per week.* *Didn't want side effects from meds daily.* *Rebif was one of the less "invasive" drugs - by that I mean the side effects were less serious than that of stronger drugs such as Tecfidera. Plus, it was recommended by my neurologist.* *As I had a low white blood cell count and digestion issues we felt Copaxone would be the best drug for me.* MS specialists: *I can foresee patients having to transfer onto a more expensive drug after failing on Extavia rather than trying an alternative injectable. They will then be forced to choose one of the oral drugs and accept their associated risks and monitoring even if this impacts upon their daily life and causes anxiety regarding possible severe side effects.* *The side effects should be considered - an injection of interferon every other day is less tolerated than an injection every two weeks or glatiramer acetate every day. Cost-effectiveness should include the costs of managing side effects and the effect of side effects on employment.*
3.4	**Severely limited choice** With this recommendation, NICE is proposing that treatments available to people with active relapsing MS would be: interferon beta 1b (Extavia), teriflunomide (Aubagio), dimethyl fumarate (Tecfidera) and alemtuzumab (Lemtrada). Teriflunomide, dimethyl fumarate and alemtuzumab are each associated with side effects which may make them unsuitable, particularly for those with comorbidities or those who are risk averse. People taking one of these first line treatments may experience an adverse event such as liver injury or prolonged lymphopenia and be unable to continue taking the drug. They will have greatly limited choice if Extavia is the only injectable treatment available to them, with the risk that they may not take up or may discontinue treatment entirely. 16% (82/522) people with MS responding to our survey raised the issue of severely limited options if Extavia was the only injectable disease modifying drug. 26% of health professionals responding to our survey specified concerns that the decision limited patient options. MS specialists: *People who require first line treatment and cannot tolerate the oral medications will have limited options.* *Limited choice. Extavia is more difficult to tolerate than some of the other injectables.*
3.5	**Drug safety monitoring**

	The proposed first-line treatments require more frequent blood and urine tests to monitor for potential side effects. For many people, this will mean a visit to a hospital clinic which is often disruptive for family and work commitments and can involve significant travel costs. Glatiramer acetate is often preferred as no safety monitoring is required. This minimises the impact of the treatment on family and work commitments. In addition, the focus of health professionals to manage the increased monitoring requirements impacts on people with MS who may have to wait longer for review appointments or when experiencing a relapse. 2% (9/522) people with MS specifically cited lack of monitoring on Copaxone as reason for choice People with MS: *It [Copaxone] suited my lifestyle. No monitoring, wouldn't get in way of my job.* *I chose Copaxone because I was in full time work and it was simple, no significant side effects and no need to take time off work for blood tests.*
3.6	**Use of treatments during conception and pregnancy** **We consider that the proposal to recommend Extavia alone is discriminatory towards women of childbearing age who intend to conceive, as it will remove all appropriate treatment options.** The committee rejected equality considerations concerning safety of glatiramer acetate during pregnancy based on the wording of the marketing authorisation. The committee will be well aware that the wording used is routinely hypercautious. There is now substantial data to show that glatiramer acetate can be taken safely during pregnancy, reflected by the fact that this is now well-established in clinical practice. As noted by a neurologist responding to our survey: "The exclusion of Copaxone would be a particular loss to women wanting a safe disease modifying drug during pregnancy - for which this drug is now routinely used in some centres." The proposed first-line treatments Extavia, teriflunomide, dimethyl fumarate and alemtuzumab all carry significant risks during pregnancy and are contraindicated. 3% (14/522) people with MS responding to our survey raised the issue of conception and pregnancy as a consideration when choosing an injectable disease modifying drug. 17% (20/122) of HPs responding to our survey raised the issue of conception and pregnancy as a consideration when choosing an injectable disease modifying drug. People with MS: *First of all, the worst decision would be rejecting Copaxone. As far as I know it is the only drug for people with not very active MS that can be taken while pregnant or breastfeeding.* *Upset. 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.* MS specialists: *These recommendations are a harmful retrograde step in the management of patients with MS. They completely remove from patients the ONLY licensed treatment with evidence of safety during pregnancy (copaxone). Because of this I consider the recommendation to be discriminatory on the grounds of gender.*
4	**Impact on MS services**

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4.1	**Greater costs for NHS and social care systems** Many people are not happy with the higher risks and possible side-effects associated with the proposed first-line treatments for relapsing MS. Faced with a choice between frequent injections and the flu-like side effects of Extavia and the higher risk side effects of these treatments, many people will choose no treatment. This is likely to lead to increased burdens on the NHS due to the more rapid progression of MS – e.g. more GP and consultant appointments; more time needed with specialist nurses; greater pressure on social care and family care systems; more unplanned hospital admissions etc. MS specialists: *Limiting the options to one drug is likely to limit uptake of treatment at this stage, which may have implications for future disease activity and disability.* *It may result in short term savings but is likely to increase long term costs with treatment failure and escalation.* *Absolutely shocking decision that will cause disabling and distressing relapses resulting in an increase in the need for symptom management, rehab, social care and benefits.*
4.2	**Patient care** People who struggle with manual dexterity, visual or cognitive issues will require additional support from MS services to manage their treatment. In addition, the drug monitoring requirements of the proposed alternatives impact on the health professionals who support people with MS. The time taken to carry out the higher level of monitoring will increase the pressure on an already overstretched workforce. As a result, other patients may have to wait longer for appointments or the costs of additional staff to manage the workload will be incurred. MS specialists: *More clinic time for reviewing and possible administration due to poor dexterity.* *We would get an increase in calls, patient visits and a lot of complaints.*
4.3	**Lack of Patient Support Programme** Extavia has a very limited patient support programme. This will put extra pressure on the MS nurses to train people when they start injecting and support them when they have problems with side effects or injection technique. MS specialists: *Many patients cannot do this [make up treatment] and cannot rely on others to do it. I am sure that GP services would be unable to accommodate alt[ernative] day injections being administered, nor could the district nursing teams. Within MS we teach a self-management approach to wellbeing and the choice of drugs has been an integral part of this, it helps with adherence to medication, I truly believe that we reduce wasted medication costs to the NHS when taking into account choice of DMD.* *They would not get the support that the other drug companies offer (nurse support package).*

	Novartis DO NOT provide training demo kits for patients any more. So we cannot train our patients! *If Extavia became the only therapy option for RRMS, we would be unable to continue supporting patients at home with Injection training and follow on support and care. This would have a huge impact on the MS Specialist Nurses who would then have to train all patients in their clinics resulting in a huge increase in their already overburdened workloads.*
4.4	**Increased demand for oral treatments** The decision to recommend Extavia alone will increase demand for teriflunomide, dimethyl fumarate and alemtuzumab. This will place increased pressure on over-stretched services in order to initiate treatment, provide side effect management and drug safety monitoring. MS specialists: *I can foresee patients having to transfer onto a more expensive drug after failing on Extavia rather than trying an alternative injectable. They will then be forced to choose one of the oral drugs and accept their associated risks and monitoring even if this impacts upon their daily life and causes anxiety regarding possible severe side effects.*
4.5	**Management of patient expectations** Specialist MS teams will need to deal with the problem of treating patients who will be offered different treatments according to the date their MS was diagnosed which will add to the complexity of managing disease modifying drugs within the MS service. Health professionals will need to explain the lack of treatment options to newly diagnosed patients, placing them in potentially upsetting and difficult positions and ultimately leading to increased pressure on services. It may also lead to lower staff morale, as specialist teams will be unable to offer what they consider as better or more appropriate treatment options, and will be unable to provide high standards of care due to increased workload. MS specialists: *I think many MS people would be unhappy due to side effects etc., and would be calling in for assessment and advice which would ramp up pressure to our already stretched out services.* *I feel this is very poor judgement on NICE's part. By limiting the options to patients you are causing wider problems in the long term. NICE continually recommends treating patients as individuals and tailoring their care to them then proceeds to offer a 'one treatment fits all' approach. This WILL have a negative impact on drug compliance, reduce patients' options when they have a reaction to extavia and put over-whelming pressure on a delivery service that already messes up orders.* *Medications that are already a reminder of having MS need to fit in as seamlessly as possible with someone's life for them to feel comfortable with it, for them to be accepting of side effects and for them to stick with it. I think there are very likely to be more switches to other treatments and therefore ultimately cause disruptions to patients and add to the workloads of already stretched services.* *The most important thing is being able to offer people with MS choice of treatments so as we can work collaboratively to find the most effective treatment that they can tolerate, administer with least effort and minimal if any side effects. We can only do this if we have the range available.*
5	**Overarching criticisms of the appraisal**
5.1	**Lack of transparency**

	The proposal to recommend Extavia alone is based on cost-effectiveness. However, as the ACD states, the drug costs are 'commercial in confidence'. This means that stakeholders and members of the public are not able to evaluate the most important issue governing the Committee's decision to approve Extavia and reject the remaining five drugs. It is also unclear to what extent the manufacturers have been able to participate in negotiations over patient access schemes and discounts. None of these discussions have been conducted in the public domain.
5.2	**Best supportive care** NICE has compared the cost of the beta interferons and glatiramer acetate with best supportive care, and found Extavia alone is cost effective. No details are given of what would constitute "best supportive care". The MS Trust and other stakeholders have raised the issue of best supportive care as a comparator in previous single technology appraisals: it has been rejected as a comparator because (1) it is not an option in current clinical practice, (2) the concept is idealistic because in reality people with MS often have very limited access to services, (3) there is no consensus on what best supportive care is and how much it costs, and (4) it is inconsistent to compare the cost of a disease modifying drug which has a constant cost regardless of location with a comparator which would vary locally since there is no mechanism to ensure that best supportive is consistently implemented. Moreover, in reality, those people for whom Extavia is not appropriate (for reasons outlined above) would instead be offered either teriflunomide, dimethyl fumarate or alemtuzumab. Assessing the beta interferons and glatiramer acetate against best supportive care may have been appropriate when the original TA32 appraisal was carried out more than fifteen years ago, but the committee will know that the treatment landscape for relapsing MS has moved on dramatically since that time. For the purposes of understanding the true cost to the NHS of decisions made in this appraisal, the drugs should be compared to the current, alternative treatment options people will actually be offered; best supportive care is not one of these. Recent single technology appraisals have acknowledged this new treatment paradigm and have made decisions based on cost effectiveness compared with active treatment (dimethyl fumarate TA320, teriflunomide TA303, alemtuzumab TA312). Comparison with best supportive care unfairly disadvantages beta interferons and glatiramer acetate in this appraisal.
5.3	**More costly alternative treatments** Those people for whom Extavia is not appropriate would instead be offered one of the other "first line" drugs - either teriflunomide, dimethyl fumarate or alemtuzumab. These drugs are more costly and require more safety monitoring than beta interferons and glatiramer acetate; the net effect of the ACD decision will be greater cost to the NHS.
5.4	**Innovation** Section 3.2 of the ACD states: The committee understood that its remit was to revisit the original appraisal, and to compare beta interferons and glatiramer acetate with best supportive care, rather than with the newer drugs. Section 3.25 states: The technologies are no longer considered innovative.

Consultation on the appraisal consultation document – deadline for comments end of 24 January 2018

	By comparing the drugs to best supportive care, the alternative treatment option which applied at the time that TA32 was undertaken, but on the other hand refusing to recognise the innovative nature of the treatments which applied at the time that TA32 was undertaken, the appraisal committee is employing double standards. When compared to best supportive care, all of the treatments under appraisal should be considered innovative. Since TA32 was carried out, both Avonex and Rebif have been reformulated to improve their tolerability and immunogenicity. There have also been significant enhancements in the autoinjectors for these two beta interferons which greatly improve patient adherence and therefore clinical efficacy. Although Plegridy has been included in the review of TA32, it is actually a new product, using pegylation to extend circulating half-life and therefore reduce injection frequency making it an attractive option for patients. Finally, Copaxone has been reformulated to provide an alternative dosing schedule, three times weekly in addition to the daily injection frequency. In contrast, there has been limited development of Betaferon and Extavia. Long-term commitment to developing and improving a product should be considered when making this recommendation.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments end of 24 January 2018

Please return via NICE Docs

- **NICE consultation on the use of beta interferons and glatiramer acetate for treating multiple sclerosis: Responses from people with MS gathered by the MS Trust**
- **January 2018**

In December 2017 NICE published a consultation on the use of beta interferons and glatiramer acetate for treating multiple sclerosis. To inform our response to the consultation, the MS Trust carried out two surveys to gather views on the recommendations made by NICE - one to gather the views of people with MS, and another of specialist MS health professionals.

- **This document presents some of the issues raised by people with MS in response to the consultation recommendations.**
- **The overwhelming majority of people disagreed with the recommendations made by NICE.**
- **Of 522 respondents, 8 agreed with the NICE recommendations.**
- **Only two people who responded to the survey are using or have used Extavia. All other respondents use or used a different DMD.**
- **While this is a lengthy document, we feel it is necessary to demonstrate to NICE the strength of feeling regarding the consultation recommendations, and to allow the people who responded to our survey to have their voices heard.**
- Pages 2 and 3 provide a table summary of the issues raised.
- Pages 4 to 36 demonstrate people's experiences on each of the beta interferons and glatiramer acetate.
- The survey of people with MS was carried out on SurveyMonkey between 20 December 2017 and 10 January 2018.
- 522 people responded to the survey.
- Some respondents may also have responded to NICE directly.
- Some statements have been used more than once in the data below as they address multiple issues.

Summary of the issues raised in our survey of people with MS	
Issue:	**Our survey results show that:**
1. Lack of choice / restriction of options	• People with MS are **worried and angry** that the NICE recommendations will **remove choice for first line treatments, both for newly diagnosed patients and for those who need to switch treatments**. • People with MS see the recommendations as a **short-sighted** cost-cutting exercise which, in the longer term, **will place additional pressures both on the NHS and the state**.
2. Side effects and tolerance	• **There is no 'one size fits all' when making decisions about treatments for MS. People with MS react differently to different treatments, which is why a choice of treatments is essential.** • Our survey results show that **consideration of side effects plays a huge part in people's choice of treatment**. • **Many people with MS suffer from side-effects when using DMDs**. • Many people make **treatment decisions based on the side effects of treatment schedule** – i.e. by taking Plegridy once a fortnight or Avonex once a week, people can limit their side effects to the time around administration. • Other people **make treatment choices which require more frequent administration, as using a lower dose more frequently suits some people better** as they experience fewer or no side effects. • **Limiting the choice of self-injected treatments to Extavia will mean that many people with MS will have no option but to use the oral and infusion treatments,** if applicable, and accept the side effects associated with these. It is likely that **for some people, these will be intolerable, and they will stop all treatment.**
3. Ease of use / administration	• **Ease of use and administration of injectables plays a key part in people's decisions** about their treatment. • Many people do not like injecting, and choose their treatment based on needle size or because the injectable device hides the needle, making an injection schedule tolerable. • Many existing injectables are administered using a pre-filled device, making injecting easier. • Many people appreciate and make use of the support package that comes with their treatment.
4. Injection frequency	• **Injection frequency plays a huge part in people's treatment decisions.** • **Injecting every other day, as required with Extavia, is not suitable for many people with MS.**

Summary of the issues raised in our survey of people with MS	
	• A **requirement to inject frequently**, as with Extavia, is likely to lead to many people suffering from **injection site issues** and **stopping treatment**. • **Injecting every other day will not fit with many people's lifestyles**, as they will not have the **time to inject** or be able to **cope with frequent side-effects**. • Some people with MS are **needle-phobic** and would not be able to use Extavia, limiting their choice to oral treatments or no treatment at all.
5. Switching to different treatments	• Many people with MS **start on one treatment and then switch to another** if they find that it does not suit them. • Many people switch between first line treatments and have found the choice to be crucial to maintaining their lifestyle
6. Suitability of treatments due to co-morbidities and risks, including pregnancy	• Many people with MS **are unable to take some of the treatments on offer because of pre-existing conditions.** • **Therefore, having a choice of treatments is crucial so that people are able to find one that is suitable for them.** • **Many women with MS choose to take Copaxone during conception and pregnancy as it is the only suitable treatment.** • **Some people are not prepared to accept the risks associated with the highly effective treatments, even if they are eligible for them**
7. Staying in employment	• **The ability to stay in employment plays a key part in people's decisions about their treatment.** • **Many people with MS feel that their experiences on the DMTs has allowed them to stay in employment.** • **Many people feel that without the use of DMTs they would become a 'burden' on the state both in terms of claiming benefits and more frequent NHS visits.**

1. Lack of choice / restriction of options

Our survey results show that:

- People with MS are **worried and angry** that the NICE recommendations will **remove choice for first line treatments, both for newly diagnosed patients and for those who need to switch treatments.**
- People with MS see the recommendations as a **short-sighted** cost-cutting exercise which, in the longer term, will place **additional pressures both on the NHS and the state.**

Survey results:	**35% of respondents** (182/522) stated that the NICE recommendations would remove choice and narrow options for people with MS.
What did people with MS say about this:	**People were asked:** • **How they felt about NICE's recommendation of Extavia, but rejection of Copaxone, Avonex, Betaferon, Plegridy and Rebif?** While we have not listed all the responses that mentioned lack of choice and restriction of options, the statements below help to demonstrate the strength of feeling that respondents showed to the NICE recommendations. MANY responses echoed the following sentiments: • I think that it is **appalling to withdraw options and choice** for both patients and those treating the patient. Rounding-up all patients - who have varied disease stages and requirements - into the same 'truck' is immoral, insensitive and damaging. • **Absolutely disgusted that I am not worthy of therapy many others have received for many years.** • **A poor decision**. Each drug is different and will be react differently to each person. **Everyone should have the choice** of any of the drugs without restrictions. • This is **taking away patient choice** and going against government policy of patient being at the centre of their care and self-management. • I think that it's **appalling that newly diagnosed patients are now denied access to 5 medicines which could work for them,** without considering tolerability, safety and efficacy (surely the most important considerations for patients and prescribers) when making the decision not to recommend them!

	• **I am utterly dismayed** that the decision to stop these life changing drugs being available has been made. It will have a catastrophic effect on those newly diagnosed and **will rid people of the right to choose a first line of treatment that is so important to so many.** • **There is no one treatment that suits all and as long as the existing treatments are effective then they must continue to offer them to new patients** as well as allowing those already receiving treatment to continue as long as they need to. • **Everyone should have a choice as everyone reacts differently** and has different lifestyles. • **NICE have yet again demonstrated that they know the cost of everything and the value of nothing**. NICE can longer be trusted to be make the right decision. • The decision has been **based purely on cost** and allowing Extavia to control the market is not good. • I believe that it is **incredibly short sighted of NICE** to only recommend one disease modifying medication for MS. On a personal level I feel incredibly let down by NICE **who appear to have put cost over patient benefit.** • It is very disappointing that **NICE is eliminating the choices available to patients and neurologists purely based on cost.** • Appalled. **NICE have failed to understand the long term implications for people with MS. Less availability of DMD on the NHS will result in more hospital admissions, causing greater strain on the NHS.**

2. Issue: side effects and tolerance

Our survey results show that:

- **There is no 'one size fits all' when making decisions about treatments for MS. People with MS react differently to different treatments, which is why a choice of treatments is essential.**
- Our survey results show that **consideration of side effects plays a huge part in people's choice of treatment**.
- **Many people with MS suffer from side-effects when using DMDs**.
- Many people make **treatment decisions based on the side effects of treatment schedule** – i.e. by taking Plegridy once a fortnight or Avonex once a week, people can limit their side effects to the time around administration.
- Other people **make treatment choices which require more frequent administration, as using a lower dose more frequently suits some people better** as they experience fewer or no side effects.
- **Limiting the choice of self-injected treatments to Extavia will mean that many people with MS will have no option but to use the oral and infusion treatments,** if applicable, and accept the side effects associated with these. It is likely that **for some people, these will be intolerable, and they will stop all treatment.**

Survey results:	**35% of respondents (182/522)** stated that consideration of side effects played a part in their choice of treatment, and in their decision to stay on a treatment.
What did people with MS say about this:	**People were asked:** • **About their experiences on Avonex, Betaferon, Copaxone, Extavia, Plegridy and Rebif** • **Why they chose their treatment** • **Why they continued to take it (if applicable)** **General comments on side effects:** • **Everyone should have a choice as everyone reacts differently** and has different lifestyles. • I feel that these drugs, although comparable in efficacy, are not comparable in terms of either administration, tolerance etc, and therefore **it seems very narrow minded to assume that one drug fits all**. • It also needs to be taken into account that **all MS drugs have significant side effects** or potential problems with methods of administration so the **narrowing of drug choices available at this time limits options for those who may have struggled with other drugs**.

	<u>On Avonex:</u> • I **do not feel lasting side-effects.** • Avonex and Plegridy. Some side effects of each, particularly initially, but **manageable**. • The Plegridy/Avonex **side effects appeared to only be minimal** and should be **manageable** & **short term.** • Thankfully I had **no side effects** so have stayed on it for the last 5 years. • First 18 months very bad flu like side effects experienced but **now ibuprofen taken limit these.** • Avonex - I've been on this drug for 4 years with **no side effects and no relapses**. • It worked for me with **little side effects.** • I chose it because of the convenience of it being once a week and **lack of side effects.** • Avonex. **Never had any bad side effects** with this drug. • The known side effects **I decided I would manage effectively.** • I felt flu like side effects during the night of administration, and sometimes the next day, which is frustrating, but **it is ok as it is only one day per week.** • **Didn't want side effects from meds daily.** • Very **limited side effects**. • Ease of use and **least side effects** • I chose the drug because I knew others on the medication and because it was once a week with **fairly tolerable side effects.** **<u>On Copaxone:</u>** • I looked at the side effects and made my choice based on those. • On Copaxone the **side effects were less**. • **Minimal side effects**. Stable lesion. • Copaxone is great, **no real side effects.** • I inject Copaxone daily and have **no side effects.** • Based on thinking through options available chose Copaxone as it **did not cause flu symptoms** on injection days. • It had **the side effects I felt I could best cope with** of all the options. • I've been using Copaxone for 7 months now and found it very easy to use with **no noticeable side effects**.

	• I took Copaxone for a number of years because I chose to take a drug that was **less likely to cause significant side effects.** • I decided on Copaxone because it had **less side effects associated with it**. • I do have some **minimal side effects, but they are completely manageable.** • It had **less side effects** than some of the other options. • I have **no side effects which was one of my main reasons for choosing it.** • Copaxone - positive experience. No relapses, **minimal side effects** only slight sore reactions in early days. • The **potential side effects were less worrying** and **I didn't want to have regular blood tests** to check liver function etc. • Copaxone was an effective preventative with **few side effects.** • I am currently on Copaxone. I made this decision on diagnosis based on the **lack of side effects** and am doing well on this. • I have used Copaxone since diagnosis in 2010 & have been relapse free with **no side effects**. • Less side effects. • Copaxone had the **best risk/benefit profile for me**. • **Less side effects** than many of the other DMD options. • Most effective at the time- **least side effects.** • I have not had an attack for years now, thanks to Copaxone with **little side effects**. • **Fewer side effects.** • **Least number of side effects**, ease of use. • Because it was **a drug that has proven its safety and effectiveness** over many, many years of use. • **Less side effects** and a **starter drug so plenty of other options it didn't work**. • I chose Copaxone because I was in full time work and it was simple, **no significant side effects** and no need to take time off work for blood tests. • Copaxone..... I believe it has helped me and with **less side effects/ bad reactions**. I'd rather the devil I know to be honest. • Copaxone, **despite having one possible nasty side effect, appealed to me** because it would not leave me with flu-like symptoms and needing to take additional medication to combat it. • Wanted to start Copaxone due to side effects.

	• Easy to take and **fewer side effects**. • Copaxone works well for me with **very few if any side effects**. • When researching the drugs on offer to me- **this one had least side effects**, so I can continue in full time work. • After talking with my MS Nurse who advised it as it's got **less side effects.** • Least side effects. • No side effects. • Copaxone give me **no side effects** at all • Because it had the **least side effects**. • No side effects • No side effects for me to deal with. • Copaxone was great compared to other disease modifying drugs, **I have no side effects** and I haven't had a relapse since starting the medication. • I am choosing Copaxone because it is the most appropriate for me, to allow me to lead my currently healthy lifestyle **without adverse implications from certain side effects.** • I felt Copaxone had lesser of side effects. • Copaxone has been brilliant, with **few side effects** and I could integrate it will into my life, and get on with my life. • I have been on Copaxone for quite a few years have **not suffered any side effects** and had two relapses. • Copaxone is working for me, **minimal side effects** and no relapses. • I've taken Copaxone. With **no side effects at all**, it was a very effective treatment for several years. • Least side effects. • It also holds the **fewest side effects** in comparison to the beta interferons. • I chose it because it had the **least side effects of the DMTs available to me** and as I am a single, working mother, it was important for me to be able to continue my life as normally as possible. • Because it came with **less side effects** than the other options. • **Copaxone does not suppress immune system**. The way it works will constitute the best and the safest option for me. • No relapses on Copaxone. **No major side effects**. Means I can still work.

	• Due to it having the **least amount of side effects.** • My neurologist and I both felt that this was the best for me as it has **no side effects** and the best one to reduce releases. • It seems to have **minimal side effects**. Allowing me to still work full time and get on with a busy life. • Find Copaxone very easy to use **without any side effects** made a huge difference to me. • However one of the big reasons for choosing it was because it had the **least amount of side effects** and was generally well tolerated. • Copaxone is great, **no side effects**, no relapses. **<u>On Plegridy:</u>** • **Very minor side effects**. • **Fewer side effects.** • The side effects appear **manageable**. • Avonex and Plegridy. **Some side effects of each, particularly initially, but manageable**. • The side effects I found quite bad at first but **as time goes on they are not as bad**. • The Plegridy/Avonex **side effects appeared to only be minimal and should be manageable & short term.** • The **potential side effects were less extreme** than a lot of the other drugs. • Less frequent injecting and **no tummy upset listed as side effects.** • I currently use Plegridy and **after a period of adjustment with regards to side effects I now feel that it has a minimum impact on my life.** • Because it was less invasive being an injection once a fortnight and **the side effects were the best of a bad bunch in my opinion.** • Plegridy has always worked well with me. **I have never had any bad side effects**. • **Minimal side effects.** • **Despite side effects Plegridy has lessened my fear of a relapse** so that I am now able to live a normal life without restricting myself. • As it had **less side effects** than others.

	<u>On Rebif</u> • My 13 year old daughter has been on Rebif for a few weeks having been diagnosed with Ms fairly recently. She is doing very well and **doesn't seem to be suffering any side effects at the moment** • Other than site injection problems there has **been no other side effects.** • Because of side effects. • Rebif has been really helpful to me and since taking this the **side effects have been minimal** • **Minor flu like side effects controlled with ibuprofen.** • It has suited me - **no side effects** and no relapses. • Minimal symptoms. • I have got on with it really well with **minimal side effects**, and I feel very fortunate to be on it as it seems to have kept my MS at bay over the years. • As it worked for me. **Never suffered from any side effects.** • The **possible side effects also seemed to be ones I could tolerate** and continue working. • **Few side effects** and a noticeable improvement in the progression of my MS • I chose this drug because there wasn't **hardly any side effects**. • I had to inject myself with a combination of Rebif and Betaferon, **there were side effects but these were acceptable considering the other option of not being able to function and contribute to society.** • Have been very happy with the drug and have **never experienced any side effects**. No major relapses since 2007 speaks for itself. • Have been on Rebif for several years. **Apart from flu like symptoms (which are easily managed with Nurofen) and red site reactions I have had no problems on it.** • I have been fairly stable for a number of years, I am used to self-administering it and **I don't get any side effects.** • **I weighed up the benefits against the side effects** and felt I wanted to lessen the progression of my MS if I could. • I use Rebif and find that **the side effects are minimal**. • **No side effects** and MRI results are good. • It had the **least risks and least side effects**. It was also recommended by my neurologist. • **The side effects were limited** which is always important.

	• **Rebif was one of the less "invasive" drugs - by that I mean the side effects were less serious than that of stronger drugs such as Tecfidera.** Plus, it was recommended by my neurologist

3. Ease of use / administration

Our survey results show that:

- **Ease of use and administration of injectables plays a key part in people's decisions** about their treatment.
- Many people do not like injecting, and choose their treatment based on needle size or because the injectable device hides the needle, making an injection schedule tolerable.
- Many existing injectables are administered using a pre-filled device, making injecting easier.
- Many people appreciate and make use of the support package that comes with their treatment.

However,

- Administering Extavia requires good dexterity, vision and cognition as:
- The Extavia injection device can be seen, whereas with other treatments, the device is better designed for self-administration and the needle hidden.
- The needle used for injecting Extavia is not pre-filled, requiring a 17-step process to administer the treatment.
- Many people with MS will find this process difficult or impossible, leading to decreased efficacy of the treatment and increased numbers of people dropping out of treatment.
- Extavia does not have a support programme to help people adhere to their treatment regime.
- Limiting the choice of moderately effective drugs to Extavia is likely to lead to many people stopping treatment due to problems with making up the treatment and adhering to the injection schedule.

Survey results:	**13% of respondents** (72/522) stated that ease of use and administration played a part in their choice of treatment.
What did people with MS say about this:	**People were asked:** • **About their experiences on Avonex, Betaferon, Copaxone, Extavia, Plegridy and Rebif** • **Why they chose their particular treatment** • **Why they continued to take it (if applicable)** **General points about administration:** • Decisions on which DMD to take are taken with **consideration to cognition, life style, residual impairment such as dexterity, memory etc**.

	• This is a very bad decision for patient choice. It **ignored the different application methods** and frequency and takes away the ability for patients to select a drug. • All MS drugs have significant side effects or **potential problems with methods of administration** so the narrowing of drug choices available at this time limits options for those who may have struggled with other drugs. **<u>On Extavia: only 2 people of 522 stated that they took Extavia, and NOBODY chose Extavia for ease of use</u>** • They should **try mixing Extavia with gloves on**. Hopefully they will realise how **difficult** it can be for people with **reduced dexterity due to lack of sensation in finger tips.** **<u>On Avonex</u>** • It was important to me to have a drug which required **minimal daily effort** (Avonex is weekly) so that I am not constantly forced to face my disability any further than my usual pain management. • It fitted in my lifestyle - I chose to take the drug **once a week so I wouldn't be constantly thinking about it and my fear of needles**. Also it goes straight into the muscle so does not cause any discomfort. I'm **completely comfortable with this drug and administering it**. I'm used to transportation on flights too. • **The injection pen was helpful as I was nervous doing injections**. • I chose Avonex as it's only once a week and **easy to do** • I chose Avonex as it is administered weekly, so I only really have one bad day per week… MS can impact life significantly on daily life, the choice of medication allows for that to be less of an impact • I take Avonex and chose this drug because **you inject with an easy to use pen once a week**. • On Avonex and Plegridy: **Injection design** and frequency of administration • Avonex - I don't like injecting, but I chose one that was infrequent (weekly) and **one that came with a "pen" to administer.** **<u>On Copaxone:</u>** • It is **easy to administer myself** • It's **easy to administer** and does not impact my daily life at all.

	• Rebif did not suit me and the schedule of injections was confusing. **Copaxone is administered daily so is easy to remember**; an important point when you consider the effect MS can have on your memory. • Copaxone is **simple to use.** • Very positive experience with Copaxone. **Easy to administer** and worked for me for 10 years. • On Avonex and Copaxone: **Easy to use,** good results, **I was in control.** • Went from Avonex to Copaxone purely because I didn't like injecting into muscle it hurt and I found myself getting into a state about doing it, **Copaxone much easier.** **<u>On Plegridy:</u>** • I take Plegridy the drug is **easy to administer** one simple injection once a fortnight. • The **ease and convenience of a fortnightly Plegridy injection** that does not need to be refrigerated for up to 28 days is a real boon and **makes my constant business travel much easier** than might otherwise be the case. • Plegrdiy is effectively the same drug as Avonex but fortnightly rather than weekly injections and also the **greater ease of administering** Plegridy injections was attractive. • I took Plegridy - its side effects were minimal. It was **easy to administer** every 2 weeks and it worked for me for a year. • Plegridy for 1 year- **easy** fortnightly injections, side effects less severe than Avonex, left with red rash around injection site for 4-5 weeks. • Very simple to use - **easy to store and transport**. • The fortnightly injections suit me because I work full time and commute a fair distance to work. Only having to manage the injection every two weeks means that any side effects are limited to every other weekend and have not impacted on my ability to work full time. **I also struggle to self-inject and the Plegridy pen makes this manageable for me.** • On Avonex and Plegridy: **Injection design** and frequency of administration

	<u>On Rebif:</u> • I take Rebif, have done for a couple of years. Taking Rebif, **using the Rebismart system is a helpful reminder of where and when to inject. It's pretty painless. Hugely convenient. The service attached to it is extremely good and worry free.** • I've been on Rebif and chose it for **convenience** (number of injections per week) and **ease of application**. The **Healthcare at Home package is excellent** and means I have never been short of the drugs I need. • **My decision was made on the injection methods and frequency**. Rebif was the one which seemed the most appealing to me and fitted best with my life style. • **Convenience** of the Rebif using the **Rebismart device**. • Good percentage in reducing relapses/reduced severity and **fairly easy to self inject**. • Ease of taking. • Because it was **pre prepared** and subcutaneous. • Avonex restricted my life. I chose Rebif 3 times a week despite being needle - phobic as I valued my freedom to not have to visit a nurse every week. In the end I didn't adhere completely to Rebif as my phobia got in the way. • I liked the fact it was only 3 injections a week and you got an **auto injector**. I'm now on Fingolimod but I would recommend Rebif as one of the better injectable drugs. • **Smaller needle** albeit three times a week, came **already filled**, I could and still self-inject especially **as I have dexterity issues** meant didn't have to faff about and do it myself swiftly and easily. Still the case as **I live by myself.** • Being able to **self-administer** subcutaneous injections 3 times a week, with the **flexibility** to vary the days on which I took the injections as circumstances dictated. • It seemed the **easiest & simple** one to use • **Small, fine needles that I cannot see**. **Ease of administration**. Long history of drug. • I take three injections a week, **self-administered with pre-loaded syringes**. This fits in well with my lifestyle. • I am taking Rebif. I chose it because the injection regime fits in with my life and the **Rebismart device makes it easy for me to self-administer** • Rebif was recommended to me. This was **much easier for me to mentally cope with due to the comparable needle size.**

	• **Lack of long needle**. Ease of administration, and reported benefits. • Frequency of delivery. Method of delivery **(autojet).** • It is simple to administer and **the support available is excellent.** • Rebif meant no daily injections and the facility for **auto injectable device**.

4. Injection frequency

Our survey results show that:

- **Injection frequency plays a huge part in people's treatment decisions.**
- **Injecting every other day, as required with Extavia, is not suitable for many people with MS.**
- A **requirement to inject frequently**, as with Extavia, is likely to lead to many people suffering from **injection site issues** and **stopping treatment**.
- **Injecting every other day will not fit with many people's lifestyles**, as they will not have the **time to inject** or be able to **cope with frequent side-effects**.
- Some people with MS are **needle-phobic** and would not be able to use Extavia, limiting their choice to oral treatments or no treatment at all.

Survey results:	**20% of respondents** (103/522) stated the injection schedule as a reason for choosing their treatment, or raised concerns about the frequency of injections with Extavia. Many respondents preferred to inject as infrequently as possible to minimise side effects and injection site issues. However, some choose treatments which require injection more frequently as the lower dose minimises their side effects.
What did people with MS say about this:	**People were asked:** • **About their experiences on Avonex, Betaferon, Copaxone, Extavia, Plegridy and Rebif** • **Why they chose their particular treatment** • **Why they continued to take it (if applicable)** **On Extavia: one respondent (of the two who stated that they had chosen Extavia), said that injecting had caused skin problems in the long term:** • Extavia worked fine **until I was too bruised and skin hardened so injection liquid started coming out again**. Switched to Tecfidera, but am having problems with side effects still after half a year, so don't know what to switch to now. **Avonex:** • After a few years I was switched to Avonex which **being just weekly was much more convenient** and I experienced no side effects with it. • Was once a week.

	• **Once a week IM injection suits me and my lifestyle**. • Chose Avonex as the injections are weekly rather than daily and **it seemed an easy option**. • Because I could **inject once a week**. • **Only once a week** injection. • One weekly IM injection that **is a regime I can manage**. • **Once a week** injection. • The injections are **weekly** which suited my daughter. • I had a choice of 3 injections and **chose Avonex as it was once a week**. • I chose it because of the **convenience** of it being once a week and lack of side effects. • I took Avonex when first diagnosed because at the time there were only injections to choose from and this **had the least injections.** • Chose Avonex as **only once a week**. • It was a weekly injection, which I felt was **taken frequently enough to feel effective, but was able to fit around my lifestyle.** • **Inject weekly easier for me due to work and home life.** • Avonex currently due to **only taking once a week** plus no injection site reaction. • It is a weekly injection and I preferred that rather than daily injections. • Avonex is an injection **once a week, having 2 small children I didn't want to feel rough every day or every few days.** • Simplicity - only **one Injection a week** and side effects (I did not want weight gain or hair loss) • Avonex suited my lifestyle by administering an injection **once a week.** • Avonex - I don't like injecting, but I **chose one that was infrequent (weekly)** and one that came with a "pen" to administer. • I take Avonex and chose this drug because you inject with an easy to use pen **once a week**. • Because it was only **one injection weekly so I could still work and have a life**, didn't want side effects from meds daily. • I chose Avonex as it was **only injecting once a week** instead of Rebif's three times a week. • **Once a week** and (at the time) didn't need refrigeration. • **Once weekly** and doesn't bruise my skin like Rebif did.

	• **Convenience of once a week** injection. • Because it was **once a week** with fairly tolerable side effects I thought it was a **suitable med for my lifestyle and work life.** **Copaxone:** • I inject Copaxone daily and have no side effects. • I chose Avonex as it was one injection a week then Copaxone as it was **smaller doses everyday so it was easier for me to tolerate.** • I've been giving this now for about 12/13 yrs and gave it daily up until about a year ago when they increased the dose and reduced the amount of times it needed to be given. I now inject myself x3 a week, which after all this time is much easier. • 3 injections a week, no adverse effects, **it works very well for me** - Tecfidera not suitable. **Plegridy:** • Plegridy suits my lifestyle as **I only inject once a fortnight** and the side effects for me are virtually non-existent. This **means I can continue to balance a full time job and raising my family** with minimal disruption. • I chose Plegridy because the **injection was less frequent**. • The **two weekly injections fit into my lifestyle well**. • Easy to use with fortnightly doses • I chose Avonex initially as injection was weekly and the least invasive to my life. The same decision I made when swapping to Plegridy which was a **fortnightly** injection. • I am considering Plegridy as it is **once a fortnight** and the side effects appear manageable. • I have taken both Avonex (the unmixed solution version) and Plegridy. **The choice has been made on grounds of what suits my lifestyle best, particularly since I travel for business a lot** and less frequent injections that do not need to be refrigerated is very helpful. • Took Avonex for 5 years but recently switched to Plegridy to allow **more flexibility** in my lifestyle. • I take Plegridy the drug is easy to administer **one simple injection once a fortnight**. • I only have to administer Plegridy **once every 2 weeks.**

	• It was easy to administer every 2 weeks. • I have taken both Avonex and Plegridy. **The option to inject only once per week, as I work full time, was my primary driver for initially selecting Avonex. Later switching to Plegridy further extended this.** If I were to suffer the flu-like side-effects every 2 days I would not be able to work full time. • Only having to inject once every two weeks is very **convenient**. • Plegridy only. **Side effects from injecting only twice a month allows me to work full time**. More frequent side effects would not. • Plegridy, although injectable which I wanted to avoid **is only injected fortnightly, and I am able to tolerate this.** Would not wish to infect more frequently. • Plegridy for 1 year- **easy fortnightly injections**, side effects less severe than Avonex, • The ability to be able to take the injection using a simple method **once a fortnight allows me to continue my work schedule with little to no change.** This in turn means my life is not as altered as it might otherwise had been. • Because it was **less invasive being an injection once a fortnight** and the side effects were the best of a bad bunch in my opinion. **MS is hard enough without the treatment also becoming a massive focus in my life.** • The **flexibility of 2 weekly injections**. **Don't have to remember daily or alternative days for tablets**. • Injections are once every two weeks instead of daily. • I was on Avonex for 10 years with no relapses or symptoms. I changed to Plegridy only because it was less frequent injections. • **Plegridy fit around my work pattern and the thought of injecting just once a fortnight was brilliant**. • I take Plegridy this is **once a fortnight and fits well into my life.** • It was **injections every two weeks, instead of weekly. From someone with a fear of needles this was a big win.** • It is **only fortnightly** and is a subcutaneous injection. • Injecting less frequently down from 3/week to 1/fortnight. • (Avonex) Suited me initially but now **happier with injecting less often with Plegridy.** • The **fortnightly injections suit me because I work full time and commute a fair distance** to work.

	• My mum has been on Rebif and Plegridy. **The Plegridy has improved her quality of life significantly. She no longer has to inject 3 times a week only fortnightly**. • Currently on Plegridy. It's my first DMD, and **I like that I only need to do it once a fortnight**. • Because it's **every 2 weeks and I wanted to continue with an interferon based drug as it's been tried and tested over many years** • I switched from Betaferon to Plegridy as **injections are less frequent** but it is essentially the same drug with the same success in preventing relapses. • Because it was to be **injected every two weeks** instead of everyday. **<u>On Rebif:</u>** • Rebif because **I felt I could cope with 3 injections a week.** • My decision was made on the **injection methods and frequency**. Rebif was the one which seemed the **most appealing to me and fitted best with my life style.** • Decided that Rebif would suit me better in that I could **self-inject x3 times a week**. • I chose Rebif 3 times a week despite being needle - phobic as **I valued my freedom to not have to visit a nurse every week**. In the end I didn't adhere completely to Rebif as my phobia got in the way. • The first, Rebif, as it had a good success rate and **I could handle the frequency of subcutaneous injections**. • **Because the idea of taking the drug during the week (three times) and having the weekend off appealed**. I didn't want to take it too frequently and **was advised that the symptoms were worse if taken less frequently.** • I liked the fact it was only 3 injections a week and you got an auto injector. • Looking at the side effects and frequency of injections **Rebif fitted my lifestyle the best**. • I chose Rebif as it was injected three times a week. Plegridy and Extavia weren't available when I started DMD's. • Rebif - fewer injections than alternatives. • Three times a week suited me at this time, with **three weaker doses as opposed to one strong dose.** • Only need to take 3 times a week (as opposed to every day). • Being able to self-administer subcutaneous injections 3 times a week, with the **flexibility to vary the days.**

	• I started on Avonex which made me feel terrible for a whole day every week. And, I did experience mild relapses. I changed to Rebif, the other option at the time, and **felt much better having the treatment spread out through the week and it's worked really well for me**. • My husband chose Rebif cos it was only 3 injections a week. • **Self-injecting 3 times a week fitted with my lifestyle and working arrangements.** • Because the choices were all injection and **it matched what I felt comfortable administering.** • I take three injections a week, self-administered with pre-loaded syringes. This **fits in well with my lifestyle.** • I am taking Rebif. I chose it because **the injection regime fits in with my life**. • Injections every other day, so have good days and bad days, and **can therefore plan events accordingly**. The ability to self-inject at home **giving me control** of my MS. • Frequency of delivery. • Rebif meant **no daily injections** and the facility for auto injectable device.

5. Switching to different treatments

Our survey results show that:

- Many people with MS **start on one treatment and then switch to another** if they find that it does not suit them.
- Many people switch between first line treatments and have found the choice to be crucial to maintaining their lifestyle.

Survey results:	• **8% of respondents** (42/522) stated that they had switched to an injectable treatment. • Most people who switched did so because they could not tolerate the side effects of their previous treatment.

	• Some people switched from an oral treatment to an injectable treatment, usually due to side effects.
What did people with MS say about this:	**<u>People were asked:</u>** • **Why they switched treatments (if applicable)** **<u>On switching to Avonex:</u>** • I started with Betaferon but had injection site reactions which gradually got worse. Also, injecting every other day was a bit of a nuisance. After a few years I was switched to Avonex which being just weekly was much more convenient and **I experienced no side effects with it**. **<u>On switching to Copaxone:</u>** • I took Rebif for a year & a half but didn't cope with the side effects. I was then given Copaxone & have taken it for the last 4 years. I have had no relapses since & **side effects are minimal. It was great that there were options open to me when one drug didn't agree with me.** • I was injecting Plegridy when first diagnosed, unfortunately the side effects put me in bed for two days every injection. Now injecting Copaxone, **absolutely no problem, so glad of medication options.** • I have taken Plegridy for two years and it has given me such bad side-effects I was forced to stop taking it eventually. I switched to Copaxone then and this is the drug I have been on since half a year now. I feel so much better on this one. **It seems I can't be taking any beta interferon drugs as my body does not seem to be tolerating them. If I haven't have the option of switching to Copaxone, I wouldn't have an idea how better life can be with just the right alternative**. • I am currently **on Tecfidera but struggling with the side effects and thinking about switching to Copaxone**. • I **started using Rebif in 2009 but it didn't work well** for me so I **changed to Copaxone** which has worked well, **without significant side effects**, for 8 years. • I was **originally on Rebif** (which I chose based on convenience) but I had **awful side effects** and had to come off it after 6 months due to debilitating flu symptoms and **developing depression** (both of which disappeared as soon as I came off it). I am now on **Copaxone** and have been for nearly 5 years. I have good tolerance with **minimal side effects** and have only had minor relapses. • I am on Copaxone. **It's brilliant and I don't have any side effects**. 2 months on Tecfidera and it nearly bored a hole through my stomach. Copaxone is better. Yeah I switched from Tecfidera to Copaxone. **On**

	Tecfidera, I was in constant agony with severe acid reflux. On Copaxone there are no issues whatsoever. It's great. Don't get rid of Copaxone! • Not having got on with Plegridy I have **changed to Copaxone** which is much better for me. • I reacted to Avonex, Rebif and other drugs but am **happily tolerating Copaxone**. • **Rebif - on it for 2yrs had to come off because of side effects** & was having too many relapses on it. **Currently on Copaxone** for last 3 years only have 1 relapse. • **Interferons exacerbated the fatigue I was already experiencing** from my MS and I wanted to continue working (as a nurse in the nhs). **Copaxone had different side effects** but mainly to do with injection site reactions. I've been giving this now for about 12/13 yrs and gave it daily up until about a year ago when they increased the dose and reduced the amount of times it needed to be given. • Because I couldn't take another due to side effects and **this works best for me and my body can tolerate it**. • Having tried other injectables unsuccessfully- I finally found one (Copaxone) that agreed with me and worked. • One of four recommended, chosen as **least likely to have side effects after poor experience with Rebif**. • **Tried Rebif** for over a year but suffered very bad side effects, so **tried Plegridy** which was just as bad. Am **now taking Copaxone as it is the only option for me**. **I am unable to use any of the more effective drugs due to other medical conditions, so the only other option available to me is Copaxone**, which thankfully I am tolerating. **<u>On switching to Plegridy:</u>** • I switched to Plegridy after **severe gastric reactions to Tecfidera**. • I am currently taking Plegridy, and have found it to be the most effective of the other treatments I have experience of. (Avonex and Betaferon). **Far fewer side effects too**. • Was on Avonex 4 years but bone pain was severe but no relapse. Been on Plegridy 2 years. **No side effects** or relapses. **<u>On switching to Rebif:</u>** • I have taken Avonex, but changed to Rebif, **as the side effects weren't as bad**.

On switching to more effective treatments:

These statements demonstrate the variety of experiences that people have with switching to more effective drugs. Some people find them very effective, and others do not.

- I **initially tried Tecfidera but although I took it for less than one week I had awful side effects including liver problems.**
- I was **unable to tolerate Gilenya or Tecfidera, both tablets made me feel extremely ill** with gastrointestinal problems, chest & cough issues I'd never had previously.
- Was on **Tecfidera** but **couldn't cope with the side effects**.
- Rebif wasn't very good for me however I used Copaxone for several years before moving into Aubagio due to problems I had been experiencing with injections.
- I was **on Tecfidera for over a year and the symptoms that should have ceased didn't in that time**. I have been **on Rebif for almost a year** and although now and then I have side effects it's by far been a much better option for me.
- I took Avonex for 1 year but due to side effects I then changed to Copaxone. I took Copaxone for 2 years until I started to relapse again and my treatment was escalated to Gilenya.
- I had varied injection site reactions, which did worsen over the time I was on Copaxone and along with a couple of relapses in 2014, ultimately led to my decision to move onto **Gilenya** instead. **This has given me mixed results,** and I am due to review this again in the New Year.
- Serious site reactions and further relapse occurred. Alemtuzumab became available which had much higher effectiveness rates.
- **Avonex had major side effects** so changed to Tysabri.
- I **changed to Gilenya as I started to get more side effects on Avonex**. If I hadn't been able to change I would have stayed on it as it helped so much with the MS.
- I **could not tolerate Avonex the side effects were awful** & had a bad relapse. I was on Copaxone for 5 years with no relapses this medication helped me a lot I am now on Tysabri as Copaxone stopped working for me. I would recommend Copaxone as there are little to no side effects.
- Was on **Copaxone for a year or so, had a couple of bad reactions and was swapped to Tecfidera**.

	• I was on **Copaxone for many years** and only came off due to having a few really bad reactions to my injections. **MRI scan did show far better results with Tecfidera however**. • I don't think it's right to reject drugs that are already available when people need to have options when not every drug is working for some but is for others. **I've tried Copaxone, Avonex, Rebif and Tecfidera. I'm now on Fingolimod and it's been the best one for me so far but maybe not for others.** • **Copaxone didn't touch my MS**. I relapsed several times on it leaving permanent disability. **Wish I could have had Alemtuzumab sooner** and not wasted time on Copaxone. • **Plegridy wasn't working so switching to Tecfidera**. However I was happy to change to DMF as it is probably more effective. • I am **now taking Tecfidera**. I found that the **injections were causing the tops of my legs to become painful due to scar tissue** and so decided that I wanted to try a tablet instead. • I have been on Rebif (2 years), Copaxone (2 years) and Avonex (7 years). **I nearly died on Rebif as I developed suicidal ideation and was actively planning to end my life**. Only the wisdom and insight of a new neurologist saved me. Copaxone was like taking water, I had relapse after relapse. And on Avonex I had relapses every 18 months until I had 2 in 9 months and my Neuro felt I was in treatment failure. • I took Rebif for 3 years and am now taking Fingo. It was a good treatment for the years I was on it but for reasons I moved onto a tablet format medication. • **I am prone to allergic reactions and worried that I would experience one or other of the skin problem or shortness of breath (I an asthmatic). I tolerated Rebif very well** and was pleased with my choice. I only switched after my neurologist recommended it following a relapsed after 3.5 good years. • Rebif was my first treatment. Didn't work for me (now on Tysabri) but the side effects are minimal.

6. Suitability of treatments due to co-morbidities and risks, including pregnancy

Our survey results show that:

- Many people with MS **are unable to take some of the treatments on offer because of pre-existing conditions.**
- **Therefore having a choice of treatments is crucial so that people are able to find one that is suitable for them.**
- **Many women with MS choose to take Copaxone during conception and pregnancy as it is the only suitable treatment.**
- **Some people are not prepared to accept the risks associated with the highly effective treatments, even if they are eligible for them.**

Survey results:	• **3% of respondents (14/522) stated that Copaxone was the only treatment they could use, due to pregnancy**
What did people with MS say about this:	**People were asked:** • **About their experiences on Avonex, Betaferon, Copaxone, Extavia, Plegridy and Rebif** • **Why they chose their particular treatment** • **Why they continued to take it (if applicable)** **On choosing Avonex:** • **It was the safest drug for me due to other conditions**. It works and minus the usual side effects with it. It controls my MS. **On choosing Copaxone:** • **Because I have diabetes and Copaxone doesn't affect my liver**. • As I had a **low white blood cell count and digestion issues** we felt Copaxone would be the best drug for me. • I **cannot do oral drugs or drugs that affect GI, so injectables are really my only option**. I react badly to the flu type symptoms, so **Copaxone is really my only realistic drug choice**. • I took Copaxone for 5 years. **I made the choice for the drug as I had experienced depression and anxiety around the time of diagnosis and Copaxone did not have these issues as potential side effects**. If Copaxone would not have been 'on the table' as a drug option I would likely have rejected medication as an option as I was so scared of the side effects of the other drugs and mental health/depression had been more disabling (at the time) than any physical symptom that I had experienced (at the time) as a result of

	my MS. I eventually continued to relapse and changed medications... twice.... I'm all for as much choice as is possible. • **Due to co-morbidities and numerous drug interactions I was limited in my choice of DMT**. I have been on Copaxone for 2 years with **very few side effects**. • I had **no adverse side effects** from Copaxone in 7 years & it worked very well for me. **Could not take beta interferons due to liver problems** & there were no other choices 9 years ago. • I was **unable to take Rebif due to other medical issues. Copaxone was the best option** with the least amount of side effects. • Because **the side effects did not include depression unlike the beta interferons as I had depression**. • Had issues with injection site reactions, **changed to Tecfidera but had come off due to JC virus and my levels of lymphocytes being dangerously low**. Back on Copaxone and working very well. • Copaxone when first diagnosed and **while I was pregnant as it was the only drug deemed safe** for me to take while pregnant. • It had the less side effects and **the risk of PML scares me**. • Had good risks vs outcomes. • Amazing and wouldn't change from Copaxone **the only one I was happy taking with no additional risks** from the DMD. • It had the highest effectiveness versus least side effects and **no risk of PML.** **<u>On conception / pregnancy (most often mentioned with reasons for choosing Copaxone):</u>** • because of the fact you are **able to still start a family / fall pregnant without drastic effects on baby** • I have taken Betaferon and Copaxone. **I did very well on Betaferon but came off it to start a family. I later started again with Copaxone but did not tolerate it well so switched again**. • First of all, the worst decision would be rejecting Copaxone. **As far as I know it is the only drug for people with not very active MS that can be taken while pregnant or Breastfeeding**. • There needs to be choice for MS patients. We don't just look at efficacy, we also look at frequency, side effects, how it fits in with our lifestyles, **whether we want to be able to fall pregnant**, whether the drug might interact with other drugs we're on or if they might have a negative effect on other conditions we might have.

	• I am currently **having a break from treatment as I have a small child that I am still breastfeeding**. No doubt I will have to consider DMDs again at some point and I would hope that all options would be available as possibly Plegridy would be my next step. • Rebif has kept me well for 11 years and **I made my decision to have a baby based on this**. • On Copaxone and whilst I do not enjoy the injections (painful and site reactions) **it's the only licensed drug whilst trying to conceive.** • Cautious acceptance **with exception of Copaxone for women wanting to have children** and people unable to tolerate beta interferon side effects. • **Robbed of making a choice to go on Copaxone as a woman of child bearing age.** • Upset. 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.** • Copaxone when first diagnosed and while I was pregnant as **it was the only drug deemed safe for me to take while pregnant.** • I have only recently been **recommended Copaxone to take throughout pregnancy as it is one of the safe medications for this** as well as being effective. • I chose Copaxone as **I am planning on having a family and it's the only drug you can take whilst pregnant.** **<u>On choosing Plegridy:</u>** • Copaxone I developed an **allergic reaction**. Now taking Plegridy and it's my 3rd try of a drug. I am happy as I have **very few side effects**. • **I was too scared to take Lemtrada or Tecfidera**, and Addenbrookes recommended I try Plegridy which would either work or prepare me to take the others. **<u>On choosing Rebif:</u>** • Side effects and what I read about the medication compared to others. **Didn't want to take a tablet or an infusion.** • I based my choice on the side effects, **choosing one which appeared to have the least chance of becoming JC Virus positive** (as my sister now is). I chose Rebif as it appeared to have the **lowest risk**.

7. Staying in employment

Our survey results show that:

- **The ability to stay in employment plays a key part in people's decisions about their treatment.**
- **Many people with MS feel that their experiences on the DMTs has allowed them to stay in employment.**
- **Many people feel that without the use of DMTs they would become a 'burden' on the state both in terms of claiming benefits and more frequent NHS visits.**

Survey results:	**8% of respondents** (41/522) stated that ability to stay in employment played a key part in their choice of treatment.
What did people with MS say about this:	**People were asked:** • **About their experiences on Avonex, Betaferon, Copaxone, Extavia, Plegridy and Rebif** • **Why they chose their particular treatment** • **Why they continued to take it (if applicable)** • **Why they switched treatments (if applicable)** **General comments:** • Short sighted, was on 3 of the drugs over an 8 year period during which I had NO hospital admission or significant relapse. **15yrs on still working full time and feel wouldn't have been in this situation without those disease modifying drugs.** • Just started scared at seeming lack of alternatives. **Without effective treatment my partner may have to stop work as I may if I have to become his career.** • I personally feel that people should be able to choose their medication based on their personal situation rather than having the choice restricted purely on cost. **I am sure that most people with MS (if they are still able to work) would prefer to make their choice on what they feel would enable to continue working**.

	On Avonex: • I took Avonex for over a year and it may me feel normal again which I hadn't felt for a long time it stopped my relapses and **gave me life back so much so I went back to work.** • It was a weekly injection, which I felt was taken frequently enough to feel effective, but was able to fit around my lifestyle. **I work full time so planned to take my medication at weekends to allow me to manage the side effects.** I had to choose my treatment, and made my decision based on the information available. • Angry and anxious. I have been on Avonex for 2 years. It would not be good if I was no longer able to have a prescription for Avonex. I would feel betrayed. **I cannot work full time but manage part time employment. If I did not take my Avonex my MS would be worse and my quality of life would certainly be affected and I would have to give up work.** • I was on Rebif for approximately ten years and have been on Avonex for the last two years. **These drugs have given me a greater quality of life and allowed me to continue working as a teacher.** • I had to wait 5 years to get Avonex and was grateful when it was finally prescribed. **It has allowed me to keep on working and being independent.** • I was prescribed Avonex to alleviate relapsing remitting MS. **It kept me healthy enough to continue working as a teaching assistant for eight years.** **On Betaferon** • Horrified. Betaferon has saved my life. **I have not needed hospital stays or visits and am able to work. I have never needed to claim benefits through having Betaferon keeping me well and mobile.** There is no cure for MS and these drugs are a lifeline. I haven't had a single relapse since being on Betaferon and am **able to work, drive, etc. so can earn an income rather than having to claim disability benefits. I therefore do not use NHS funds through illness caused by relapses.** **On Copaxone:** • It was on the advice of my consultant at Queen's Square. **One factor that was influential for me was the fact that there can be flu like symptoms as a side effect of beta interferons. Given my work that would not have been tolerable.**

	• I took Copaxone for a number of years because **I chose to take a drug that was less likely to cause significant side effects and would enable me to continue to work full time**. • I took Copaxone for 18 months. Unfortunately I developed new lesions and had to change drugs. **I chose it because I felt it was something that I could fit into my life and work.** • It suited my lifestyle. **No monitoring, wouldn't get in way of my job.** • Copaxone has **allowed me to continue working and pay taxes for the last 16 years**. • I chose Copaxone because it had fewer side effects than the other options. **I work full time. That is already difficult with MS fatigue. I would struggle if I had flu like symptoms on top of this**. • I've had RRMS for 5 years now and **since starting on Copaxone have only minor relapse I'm still working full time and well. Before starting treatment I was struggling to work and function**. **It's an expensive drug but not as expensive if I was to be off work and disable**d due to ongoing relapse and damage to the nerves, • **I chose Copaxone because I was in full time work and it was simple**, no significant side effects and **no need to take time off work for blood tests.** • Has made a massive difference to the quality of my life. **I have been relapse free for 5 years and I managed to stay in full time employment as a consequence.** • I am on Copaxone- and have been for almost 6 years. Initially the thought of injecting was scary, but with the excellent training I received- the whole process is quick and easy. **When researching the drugs on offer to me- this one had least side effects, so I can continue in full time work.** • I am appalled. As someone who was diagnosed with RR MS in 2006 and refused DMDs by choice for 7 years, I know that Copaxone then kept me stable post a very debilitating relapse in 2012 until now 2017. **I was able to work full time, paying a higher tax rate and contributing in full to my family, society as a whole. I have no doubt that without Copaxone, my MS would now be worse.** I understand given the number of MS patients and the cost that thus puts a pressure in the system. • Been taking Copaxone for approximately 18 months, prior to this I was relapsing every month, with the worst leaving me unable to walk at the age of 26. Since being on it I do have the odd small relapse which recovers quickly and I am far better for using it. **As someone that works in agriculture and can have a working week in busy times with 80+ hours this keeps me going, I try not to let MS beat me but without this drug there is no way I would manage my job**....which in the end is supplying food for OUR country.

	• Feel very upset for others that won't be able to access these drugs, as I've lived with & without DMTs being available since my diagnosis 26yrs ago and have never felt better than on Copaxone after trying interferons for a year each beforehand hand. It's all about different choices. **I also managed to stay in employment for 23 of those 26 years because of the medication.** • I have been on Copaxone since April 2012 and have not had any relapses since starting it. I chose it because it had the least side effects of the DMTs available to me and **as I am a single, working mother, it was important for me to be able to continue my life as normally as possible**. **Copaxone has enabled me to do this and to be a productive member of society, despite having MS. I have not had a single day off sick related to MS since starting Copaxone**. If I'd had to take a medication with more side effects, I may have needed time off work to deal with them and may not have been able to continue in my job. • No relapses on Copaxone. No major side effects. **Means I can still work**. • Copaxone is what I am prescribed, apart from a rare post injection reaction or the fact I have to inject daily, it seems to have minimal side effects. **Allowing me to still work full time and get on with a busy life**. • Uneasy and worried for anyone just getting an MS diagnosis. When I was first diagnosed with MS nothing was available on the NHS. Luckily that changed in time for me. **I've known MS with and without DMD's, and can say from my experience they definitely help and actually save the country money, as after 17 years I am still able to work, which is something I don't believe would have been possible without Copaxone.** **<u>On Plegridy:</u>** • Plegridy suits my lifestyle as I only inject once a fortnight and the side effects for me are virtually non-existent. **This means I can continue to balance a full time job and raising my family with minimal disruption**. • I have been taking Plegridy for just over a year with excellent results. No relapses and no side effects. The two weekly injections fit into my lifestyle well. **I work for the NHS as a manager - this drug is helping me to stay well and working. I do not claim any benefits. Plegridy is keeping me independent with no other costs for the NHS** as it is keeping me well. I have injection site reactions but these do not limit me. This drug should be available for those who fit the prescribing criteria. • Plegridy only. **Side effects from injecting only twice a month allows me to work full time**. More frequent side effects would not.

	• Shocked, working within neurophysiology in the NHS I fully understand cost, however **I don't feel this decision takes into account the social aspect of drug regimes to enable people to continue with work schedules.** I currently use Plegridy and after a period of adjustment with regards to side effects I now feel that it has a minimum impact on my life. **The ability to be able to take the injection using a simple method once a fortnight allows me to continue my work schedule with little to no change**. This in turn means my life is not as altered as it might otherwise had been. • Plegridy was my first AND admit was brilliant as it fitted around my lifestyle (work nights 4 days a week) and easy to remember to take. Had to come off due to side effects after 10 months however I could be chosen another drug which is on this list. A narrowing of choices is not the way to go. **Plegridy fit around my work pattern and the thought of injecting just once a fortnight was brilliant. I now take Tecfidera due to side effects on Plegridy. This isn't as good for my work life but I make do.** • My first year after being diagnosed I was on Plegridy. That terrifying and stressful first year causes a serious acceleration of your MS and **without this highly effective drug, I truly believe I'd no longer be working. My condition would be significantly worse, and with no government assistance with benefits (due to me not being disabled enough) there would be a real chance of me losing my house.** • I have been taking Plegridy for six months, after being diagnosed about 18 months ago. **The fortnightly injections suit me because I work full time and commute a fair distance to work. Only having to manage the injection every two weeks means that any side effects are limited to every other weekend and have not impacted on my ability to work full time.** I also struggle to self-inject and the Plegridy pen makes this manageable for me. **<u>On Avonex and Plegridy:</u>** • I have taken both Avonex (the unmixed solution version) and Plegridy. **The choice has been made on grounds of what suits my lifestyle best, particularly since I travel for business a lot and less frequent injections that do not need to be refrigerated is very helpful.** The potential lessening of choice for new patients is a retrograde and disappointing development. • I have taken both Avonex and Plegridy. **The option to inject only once per week, as I work full time, was my primary driver for initially selecting Avonex. Later switching to Plegridy further extended this. If I were to suffer the flu-like side-effects every 2 days I would not be able to work full time.**

	<u>On Rebif:</u> • I have taken Rebif for 6 years and have been relapse free. **Previously I was having at least 2 big relapses a year causing me to have a considerable amount of time off work. Since starting on Rebif this has changed.** It has also meant that I can lead a fuller life as I'm not as impaired; either in a relapse or recovering from one. Rebif has changed my life for the better and I am worried at the prospect of no longer taking it. • Self-injecting 3 times a week **fitted with my lifestyle and working arrangements. The possible side effects also seemed to be ones I could tolerate and continue working.** • **Rebif let me continue my busy life as Mum and Swimming teacher**, with few side effects. • Absolutely ridiculous decision, **a combination of these drugs allowed me to be able to work, which meant I could look after my family and not rely on handouts from the state.** I had to inject myself with a combination of Rebif and Betaferon, **there were side effects but these were acceptable considering the other option of not being able to function and contribute to society.**

NICE consultation on the use of beta interferons and glatiramer acetate for treating multiple sclerosis: Responses from specialist MS health professionals gathered by the MS Trust

- January 2018

In December 2017 NICE published a consultation on the use of beta interferons and glatiramer acetate for treating multiple sclerosis. To inform our response to the consultation, the MS Trust carried out two surveys to gather views on the recommendations made by NICE - one to gather the views of people with MS, and another of specialist MS health professionals.

- **This document presents some of the issues raised by specialist MS health professionals in response to the consultation recommendations.**
- **The overwhelming majority of respondents disagreed with the recommendations made by NICE.**
- 122 health professionals responded to the survey:
  - 61% MS nurses / 22% neurologists / 10% other (including 4 pharmacists, team coordinators, support nurses) / 4% specialist therapists / 3% DMD nurses
- We received responses from across the UK:
  - 82% England / 13% Scotland / 4% Northern Ireland / 1% Wales
- The survey asked which injectable treatments were offered:
  - 69% of respondents said their service offers all 6 injectable treatments
  - 19% of respondents said their service offers a subset of the 6 injectable treatments
  - 11% of respondents said their service offers all injectable treatments EXCEPT Extavia
  - 9% of respondents happened to mention that no one on their caseload was on Extavia
- The survey of people with MS was carried out on SurveyMonkey between 20 December 2017 and 10 January 2018.
- Some respondents may also have responded to NICE directly.

Health professionals respond to the NICE recommendations:

*'This is a **stupid short sighted decision** by economists who have no direct role in patient care. It may result in short term savings but is likely to **increase long term costs** with treatment failure and escalation.'* **Eli Silber, Consultant Neurologist, King's College Hospital**

*'Strongly disagree. This is an **outrageous proposal** that can't possibly be condoned by those of us with any knowledge of these drugs and experience in prescribing them. **I can only imagine that no-one with an MS background was present** at any of the discussion. If these proposals were to be endorsed it would be nothing short of a national scandal.'* **Anon. Consultant Neurologist**

*'A **disaster and a huge step backwards** if this happens. 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.'* **Michelle Davies, Specialist Therapist, Dorset MS Service**

*'To NICE – Please don't force this recommendation into being as it will appear to be a measure of **saving money over offering good quality treatments.'*** **Allison Smith, MS Specialist Nurse, University Hospitals of Leicester**

*'I **completely disagree**… the **range of injectable treatments offer valid and useful treatment options**… limiting the options to one drug is likely to limit uptake of treatment at this stage, which may have implications for future disease activity and disability.'* **Victoria Singh-Curry, Consultant Neurologist, Imperial College Healthcare**

Question	Summary	Quantitative evidence	Qualitative evidence
What is your reaction to the NICE recommendations? Do you agree or disagree that Extavia should be the only injectable DMD treatment* available for people with relapsing remitting MS or secondary progressive MS with continued relapses? **Excluding Daclizumab*	**98% of respondents disagreed with the NICE recommendations, and many gave explicit examples to explain their response.** A significant proportion of respondents raised concerns around compliance/adherence to taking Extavia as a disease modifying treatment, including dexterity problems and lifestyle considerations. Half of respondents raised concerns about limiting patient options, many highlighting that this could prevent people accessing treatment at all.	48% of respondents (n=58) suggested that the recommendation would limit patient options	"I believe that patients should could **continue to have the choice following discussions with their specialist nurses and neurologists on what therapy would best suit them individually**, as side effects vary considerably and can have a bearing on quality of life and **concordance to therapy**." "Very disappointed in the recommendation as it does not take into account the **differences in how treatments are administered** or the ease of use of the alternative preparations nor ability to manage potential side effects if there were to be no alternatives available"
		21% of respondents (n=25) raised concerns around compliance when taking Extavia	"People chose the other injectables for a variety of reasons e.g. less frequent injections" "…there is a vast proportion [of patients] who cannot use injection pen due to dexterity." "Extavia has the same efficacy as the other injectables, but is not chosen by people with MS as it is difficult to remember to take it being on alternate days. We now have more people on Plegridy and Copaxone. The former because of the less frequent administration and the latter due to its lack of side effects profile. This appears to be a decision based entirely on money which is not appropriate as some people who require first line treatment and cannot tolerate the oral medications will have limited options."

		12% of respondents (n=14) included concerns about patient considering pregnancy	"I disagree with the NICE recommendations, it potentially puts people at risk by limiting their choice to a medication with increased side effects and potential risk to pregnancies." "These recommendations are a harmful retrograde step in the management of patients with MS. They completely remove from patients the ONLY licensed treatment with evidence of safety during pregnancy (copaxone). Because of this **I consider the recommendation to be discriminatory on the grounds of gender**."
		5% of respondents (n=6) highlighted other cost implications of this recommendation	"Absolutely shocking decision that will cause disabling and distressing relapses **resulting in an increase in the need for symptom management, rehab, social care and benefits**." "Many patients cannot do this [make up treatment] and cannot rely on others to do it. I am sure that GP services would be unable to accommodate alt[ernative] day injections being administered, nor could the district nursing teams. Within MS we teach a self-management approach to wellbeing and the choice of drugs has been an integral part of this, it helps with adherence to medication, I truly believe that **we reduce wasted mediation costs to the NHS when taking into account choice of DMD**."

		11% of respondents (n=13) broached the fact that Extavia has some concerning side effects	""Strongly disagree. Many people on Extavia experience severe flu like side effects."
What would be the impact on people with MS if Extavia was the only injectable DMD treatment* available? **Excluding Daclizumab*	Most respondents mentioned that the recommendation would limit the options of patients, meaning that some would be unable to go on a DMD at all. Many health professionals felt that this decision would result in other costs, meaning that any anticipated savings would not reflected in reality. Other significant issues raised included that Extavia is not suitable for everyone, concerns around compliance and adherence, and concerns on the side effects of Extavia.	26% of respondents (n=31) mentioned that this decision would have other cost implications	"Less concordance with therapy **increasing risk of relapse** and the **need to put on to more expensive oral therapies**." "Limited choice particularly for people with older disease who may be considering a pregnancy or wish to avoid potential infective risks. A very small cost saving is likely to result in **more treatment failures** and escalation of therapies to more expensive therapies." "They would move on to other treatments which may not suit them as well. I doubt there will be the anticipated cost saving."
		55% of respondents (n=65) mentioned that this decision restricts patient options, resulting in some patients not being able to go on any DMDs	"Patients have all expressed that access to Copaxone, Avonex, Betaferon, Plegridy and Rebif has made a real difference to them. **Patients choose based on efficacy, side effects and lifestyle considerations. I rarely see Extavia used by patients.** Patients have the right to choose and there is a lot of research to support the use of the five excluded DMDs from an efficacy and disability occurrence point of view." "Increase in relapses due to none adherence. Increased non tolerance to betaferon. No option to change on first line treatment. **Can**

			no longer tailor to dexterity or working life. Very rigid process." "Poor patient choice which **will lead to poor outcomes and disability**." "Limited choice. Extavia is **more difficult to tolerate** than some of the other injectables."
		3% of respondents (n=4) had concerns about lack of training and education programmes around Extavia (both for patients and health professionals)	"They would not get the support that the other drug companies offer (nurse support package)." "Novartis DO NOT provide training demo kits for patients any more. So we cannot train our patients!"
What would be the impact on your service if Extavia was the only injectable DMD treatment* available? **Excluding Daclizumab*	Over a third of health professionals raised the point that the recommendation would increase pressure on the service. Significant numbers of health professionals raised concerns about adherence and patients receiving inappropriate treatments for them. Other issues raised included that there would be no options for female patients considering pregnancy, it would limit options for patients and there would be other cost impacts.	35% of respondents (n=41) said that the decision would increase pressure on the service	"I think many MS people would be unhappy due to side effects etc., and would be calling in for assessment and advice which would **ramp up pressure to our already stretched out services**." "If Extavia became the only therapy option for RRMS, we would be **unable to continue supporting patients at home with Injection training and follow on support and care**. This would have a huge impact on the MS Specialist Nurses who would then have to train all patients in their clinics resulting in a huge increase in their already overburdened workloads."

			"More clinic time for reviewing and possible administration due to poor dexterity." "We would get an increase in calls, patient visits and a lot of complaints"
		25% of respondents (n=30) mentioned that they had concerns about adherence and patients being on inappropriate treatments	"Restricted choice for patients with again **offering of maybe less suitable treatments**." "I can foresee patients having to transfer onto a more expensive drug after failing on Extavia rather than trying an alternative injectable. They will then be **forced to choose one of the oral drugs and accept their associated risks and monitoring even if this impacts upon their daily life and causes anxiety regarding possible severe side effects**."
Do you have any other comments? ***(e.g. on administering treatments, patient support programmes, Homecare delivery, lifestyle, side effects, tolerance, switching)***	A number of healthcare professionals raised the issue of associated costs, such as employment, pressure on other areas of the service and increased use of A&E. Respondents also highlighted difficulties of administering Extavia as a treatment, considerations around lifestyle for people with MS choosing DMDs and side effects.	12% of respondents (n=12) mentioned impact on other costs (e.g. employment, pressure on other areas of the service, pressure on A&E)	"I feel this is very poor judgement on NICE's part. By limiting the options to patients you are causing wider problems in the long term. NICE continually recommends treating patients as individuals and tailoring their care to them then proceeds to offer a 'one treatment fits all' approach. **This WILL have a negative impact on drug compliance, reduce patients' options when they have a reaction to extavia and put over-whelming pressure on a delivery service that already messes up orders**." "Patients will have **reduced tolerance and increased relapses causing increased hospital stay and reduction in employment**."

			"The side effects should be considered - an injection of interferon every other day is less tolerated than an injection every two weeks or glatiramer acetate every day glatiramer acetate is the only drug which is licensed for pregnancy - NICE says that it is preferable not to use it in pregnancy, which is true, but this is cannot be seen as any other drug which is NOT licensed. Clinically isolated syndrome remains as a clinically distinct condition which should be treated. **Cost-effectiveness should include the costs of managing side effects and the effect of side effects on employment**." "My main concern is that it will cost more money to the NHS in the long run as the older medications are cheaper and we are aware of the side effect profile."
		9% of respondents (n=9) mentioned difficulties with administering Extavia as a treatment	"Betaferon and Extavia did not have a popular injector." "A disaster and a huge step backwards if this happens. In my experience Extavia is often not 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**. Medications that are already a reminder of having MS need to fit in as seamlessly as possible with someone's life for them to feel comfortable with it, for them to be accepting of side effects and for them to stick with it. I think there are very likely to be more switches to other treatments and

			therefore ultimately cause disruptions to patients and add to the workloads of already stretched services." "pwMS even those early in their disease have a large amount of **cognitive challenges, so to remember an alternate day preparation is hard** as each week it would be different."
		26% (n=25) specified concerns that the decision limited patient options	"The most important thing is being able to offer people with MS choice of treatments so as we can work collaboratively to find the most effective treatment that they can tolerate, administer with least effort and minimal if any side effects. We can only do this if we have the range available." "MS is a very individualised disease and any treatment should consider that"

Appraisal Consultation Document: Beta interferons and glatiramer acetate for treating multiple sclerosis (review TA32) [809]

Response on behalf of Association of British Neurologists

INTRODUCTION

This revision from the previous assessment report proposes a significant change from current practice, and a significant shift from the apparent conclusions of the last consultation document (August 2016).

The drivers to the changes appear to be:

1. a final determination of a threshold willingness to pay / QALY – still not explicitly declared but met by only one product offered at an undisclosed price to the NHS
2. a decision to exclude CIS from the review, including all the studies done in patients with CIS who would now be classified as having early relapsing-remitting MS. It should be noted that in the previous modelling of CIS patients, the cost per QALY for this group was well below NICE's usual threshold

CONSEQUENCES

The consequences of these recommendations, if adopted in their current form will be:

1. drug naïve patients looking to start IFN/GA will be offered Extavia as the only option, using the Extavia autoinjector or manually injecting. The only available regimen for a first-line injectable will be alternate day subcutaneous injections.
2. patients switching within first-line therapies for reasons of tolerability will have Extavia as the only injectable option
3. patients already switched to an oral therapy from an injectable for reasons of tolerance, but failing to tolerate that therapy, will have Extavia as their only injectable option (the recommendations do not allow a patient to go back onto their previous therapy unless it was Extavia)

AREAS FOR COMMENT

AMBIGUITY

The recommendations in this document for using Extavia are:

- the person has relapsing–remitting multiple sclerosis or
- the person has secondary progressive multiple sclerosis with continued relapses

The marketing authorisation for Extavia is:

- the treatment of patients with relapsing-remitting multiple sclerosis and two or more relapses within the last two years

- the treatment of 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

- They are also licensed for the treatment of 'patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses'.

There is ambiguity in the wording of the recommendations –making some commenting difficult. "RRMS' as currently defined (MacDonald criteria 2017) will include many patients in the single demyelinating event category of the marketing organisation. The structure of the consultation document is consistent with the committee considering these to be "CIS" as previously defined. We would need clarification on how NHSE (and equivalents elsewhere) might interpret this wording to extend/ restrict current prescribing practice. No stopping criteria are proposed.

CHOICE

The position of members of the ABN prescribing for people with MS is that it is in patients' interest to have the widest choice of available therapies. This reflects >15 years of experience using these drugs. Immediate consequences of implementation of these recommendations would be:

1. A reduction in choice for drug naïve patients starting first line therapy or switching within level. The current choices allow patients a variety of routes (sc/ oral/ im), injection frequency (from daily to once/fortnight) and of side effect profile. All drugs are currently used across the UK, with Extavia having the lowest usage. Other products have been favoured with more accessible injection devices, a lower frequency of injection, preferred patient support programmes and the lack of need for fresh mixing of the product prior to injection. The interferons are not suitable for patients with a paraprotein. The current pattern of usage, evolved over years of shared decision making and patient/ HCP interaction in the absence of financial constraint, has shown Extavia to be the least used of the first line injectables in the UK
2. For a patient whose response creates equipoise on escalation or switch within level, the only choice now available will be to switch to a more expensive oral or infusible medication, with other injectables no longer available.
3. There will not be a first line therapy with a marketing authorisation for use through pregnancy, removing the option of treatment through pregnancy for women of child bearing age. The current alternative would be to use an intermittent monoclonal – a difficult decision given the risk profile of currently available drugs in his group

The result of these proposals will be a marked reduction in choice for patients within this level of treatment. Despite the advent of oral medication, many patients still choose an injectable, in part due to their long safety record and well established risk/benefit profile. The MS therapeutic community have widely adopted the principles of shared decision making (with widespread use of the MS Decisions website and now the MS Trust MS Decision Aid). Our adoption of this practice has been in line with core NHS principles. Reduction in the choices to patients as the net result of this work would be a retrograde step. The likely outcome will be higher use of the first line orals (dimethyl fumarate and teriflunomide) where a cheaper injectable might have been chosen.

Inevitable obsolescence at time of publication

Generics are not mentioned, with glatiramer acetate assumed to be Copaxone at its current price. The advice appears already obsolete if it does not reference, by whatever methodology is used, the price that would allow access of a glatiramer acetate into the UK health system. The EMA have accepted Brabio as “glatiramer acetate” and generic substitution is likely to be accepted. The timing of this advice from NICE, coming out at the same time as potential tendering for generics to be adopted to regional formularies, underlines the potential impossibility of attempts to apply NICE’s usual procedures to drugs at the end of their patent. By excluding “glatiramer acetate” the proposals might actually exclude a drug that is more cost-effective (at the price at which it will soon be offered) than Extavia.

Retrospective nature of process and role of RSS

The set-up of the UK RSS was an extraordinary event. It required a step of faith by the four companies involved, risking their product’s reputation and pricing model internationally to allow access of the drug to UK patients. A binding *a priori* analysis scheme was accepted and, even when changed, the companies, in good faith, accepted the revised year 4 onwards analysis plan as devised by the Scientific Advisory Group. The final 10 year results, available to NICE, essentially validate the initial pricing decisions, with a deviation score of <10% for the drugs in aggregate. This was based on an agreed 20 year time horizon with a willingness to pay £36 000/QALY. All four companies remained committed to the scheme to its conclusion and contributed to the set up and support of MS services under the terms agreed. As a result of the scheme, the UK price for these drugs is below the rest of Europe, and considerably lower than the free market price in the US. The 20 year model and £/QALY threshold used to determine the entry price of each drug were based on NICE procedures at the time of the drug launch. The current time horizon extension of 50 years is a welcome evolution, reflecting the time course of MS, but the change in willingness to pay/QALY is a post-hoc development 15 years into the widespread use of these drugs in the UK.

There would appear to be a case for basic fairness to allow the companies who stayed with the scheme to continue with the RSS price as initially modelled, in keeping with the spirit of combined risk taking which underpinned the enterprise. A unilateral shift in goalposts at this point risks jeopardising future schemes of this nature in the UK. Those who remember the

dire situation at the outset, where the UK was at risk of being the only developed country to be unable to offer these innovative therapies, continue to appreciate the courage the UK Departments of Health and companies displayed at the inception of the scheme. The manufacturers of the proposed sole drug to be available, Extavia, played no part in the scheme and did not contribute to the collection of the data which has underpinned the drugs' efficacy and allowed the cost efficacy to be estimated. This seems an unfair outcome of the scheme.

LACK OF APPLICABILITY TO CURRENT PRESCRIBING PRACTICE

A major flaw in the modelling, inevitable given the timing of this appraisal after later generation drugs have been launched, is the assumption that patients discontinue at fixed rate per annum independent of response. This is not a new technology launching in an empty space. The current use of these drugs is generally targeted towards people with milder early disease. Patients are closely monitored clinically and radiologically and non-responders are rapidly moved onto other therapies. As such, the poor responders pulling down the results will simply not continue on these drugs. Only patients who have a good early and sustained response will be left on this level of therapy. Although analysis of the RSS included an attempted "ITT" analysis to explore this, the late age and disease stage of starting patients within the scheme and the lack of suitable escalation therapies for the majority of the epoch of the scheme leave this question unaddressed.

EFFECT OF EXCLUDING THE MORE FAVOURABLE CIS MODELS

We appreciate the issue of CIS is difficult due to changing definitions.

NICE produced cost effectiveness models for the use of these drugs in CIS in the last appraisal document offered for consultation. The models showed the drugs assessed to be cost effective when started at the stage of CIS.

In early studies, using the Poser criteria, CIS will have referred to patients with a single clinical attack regardless of MR activity or CSF findings, becoming "clinically definite MS' only with a second attack. The 2001 McDonald criteria (just coming in at the initiation of the RSS) allowed a diagnosis of RRMS with a new MR lesion distant from the first clinical attack. In the 2010 McDonald criteria, patients previously classified as CIS but with simultaneous enhancing and non-enhancing lesions on an initial scan would be classified as RRMS, and in the 2017 revision, CIS with oligoclonal bands and >2 lesions in the right places, even without evidence of different aging, are now also classified as RRMS. These changes have the effect of converting most patients in traditional "CIS" studies into patients with early MS, and "time to CDMS" is simply the time between two clinical attacks.

As such, these studies may best be seen as treatment trials in early MS. What is striking is the consistently higher rate of relapse reduction treating MS at this stage, and the improved performance of these drugs in NICE's modelling when used early in the disease, rather than waiting to the point of 2 relapses in 2 years, in itself now a marker of relatively active MS. Leaving out this early treatment data has the effect of demonstrating limited efficacy of the drugs when used in an RSS-like cohort (mean age 39, disease duration 9 years). Real world studies and personal experience has already resulted in a shift in prescribing patterns in the UK to an earlier, younger group.

These recommendations will have the result of preventing demonstrably cost effective practice of early prescribing by using unmatched data from late prescribing. It is not clear why this large piece of work by NICE has not been used to inform the final advice.

POTENTIAL UNDERMINING OF NEWER DRUGS' MODELS

We acknowledge that the use of these drugs has fallen in recent years, being replaced for reasons of efficacy and tolerability by newer oral drugs and monoclonals. We recognise that the cost effectiveness models of these newer drugs is modelled on the RSS price of the first line injectables. As a community, it might be possible to create algorithms for treatment of MS which do not allow for new prescriptions of the 5 products excluded by these recommendations, but this appraisal in isolation offers no insight into what the implications may be for the availability of the newer drugs. It would be impossible, as an organisation, for the ABN to accept the adoption of these proposals without modelling of the knock-on effect on the availability of the drugs on which we are currently rely. This reflects the very unusual situation of NICE appraising a technology freely available for 15 years whose historic economic modelling underpins several generations of new technologies.

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

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments end of 24 January 2018

U	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**UKCPA (United Kingdom Clinical Pharmacy Association)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[redacted]

Please return via NICE Docs

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Consultation on the appraisal consultation document – deadline for comments end of 24 January 2018

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are concerned that this recommendation will have an impact on medicines adherence due to a reduction in patient choice. The wide range of injectable products currently available offer patients the option of different frequency of injection (daily to once a fortnight), route of injection and device all of which in this patient group and for patients with long term conditions have a large impact on medicines adherence. Extavia only provides the option of alternate day administration. If this is the only option is it likely that patients will tend to choose one of the other first line options that have easier dosing schedules, which would have a cost impact to NHS England. From practice Extavia is one of the lesser used options because patients prefer the devices for the other beta interferons.
2	We are also concerned that removing glatiramer acetate completely from availability will have a significant impact on patients. Glatiramer acetate currently is the disease modifying drug of choice in patients who are planning pregnancy, an important consideration for a large group of patients with relapsing remitting multiple sclerosis. It also has a better side effect profile, reduced monitoring requirement and tolerance for many patients compared with interferons and some of the other first line Disease Modifying Therapies (DMTs).
3	Glatiramer acetate has recently been made available as a generic product which is likely to provide a cost saving for NHS England
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We strongly support the view that patients are informed which is the cheapest injectable Disease Modifying Therapy (DMT) but should not be denied access to other drugs that may suit them better due to frequency of administration, provision of a prefilled auto injector, drugs not requiring regular monitoring blood tests and the profile of adverse effects. Adherence to the medication is likely to be affected if patients do not have a DMT that most suits them with regards to the above points.
2	We are concerned that this recommendation will affect directly those patients wishing to conceive, 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, which has recently been reflected in the Summary of Product Characteristics. Denying patients the option to use this medication if wishing to conceive could put them at higher risk of a relapse and developing permanent disability during this time period. The option of using Copaxone has particularly been useful for some patients who needed to stop their oral treatments in order to try to conceive.
3	We are concerned that this recommendation removes patient choice who often make their decision on how it will effect there lifestyle such as ease of administration, frequency and side effects. In addition to this some may have difficulty with manual dexterity and cognition which may affect their ability to administer the injection independently. This directly goes against Government policy on the patient being at the centre of their care. Extavia is more complex to administer as it requires preparation prior to administration. If people have no input into the decision making they are less likely to adhere to the treatment. Also people may decide not to start treatment therefore putting themselves at greater risk of further relapses and increased NHS costs Copaxone has consistently better tolerated compared with B-IFNs and oral DMDs. This is borne out by individual centres data and the risk sharing scheme data.
4	We are concerned that this recommendation will directly affect people with epilepsy who are advised not to use interferons therefore denying access to Copaxone affects prescribing for this group of patients.
5	We are very concerned that this recommendation only affects care in England hence creating a backward step to pre Risk Sharing Scheme where postcode lotteries determined treatment. How can this be explained to patients?
6	We are concerned that this recommendation will impact significantly on MS Services, Extavia (Novatis) do not provide Nurse training or a Nurse Support line for the product therefore local services will have a greater demand for training, injection side effects, support for users etc. this will ultimately affect adherence to the product reducing cost effectiveness totally
7	We are concerned that this recommendation has not taken into account that it is rare that a patient chooses extavia/betaferon when shown all the injectables. The main reasons for this is that it is not prefilled, the storage is bulky, the autojector is poor, and if a patient has manual dexterity problems then they are unable to do the injection. A range of DMT's is imperative to enable nurses to work with individuals to find the preparation that bests suits them for dexterity, tolerability, lifestyle

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8	We are concerned that this recommendation lacks consideration given to the varying side effects and the patients' tolerability of these side effects which is different for every individual. Unlike the B-IFNs, copaxone does not produce NABs.
9	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. Reducing the choice of medication will ultimately increase the blood monitoring burden on already over stretched services with a potential for serious untoward incidents resulting in patient harm.

Insert extra rows as needed

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Comments on the ACD Received from the Public through the NICE Website

Role	Patient
Other role	
Organisation	Kam
Location	England
Conflict	No
Notes	

Comments on the ACD:
Shocking idea.
Copaxon has a very good safety profile and works in a different way than other treatments. Not everyone needs to get on newer unsuitable treatments (Lemtrada etc)
This would significantly limit the choice for patients and would dramatically limit their quality of life.

Role	Patient
Other role	Staff Nurse
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:
I am very concerned about the potential decision to remove these drugs from use within the NHS, having taken 2 of these treatments I am still able to work as a nurse and believe these drugs are important in maintain health & delaying disability in many young people. Please reconsider.

Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:
I am emailing with my views about the proposal to stop offering newly diagnosed MS patients Rebif, Betaferon, Avonex and Copaxone. I was diagnosed with CIS in January 2017 with a high chance of conversion to MS. I started on Rebif in February. However, Ive stopped this recently due to low wbc and am awaiting bloods and review in 2 months. Will my neurologist be able to restart Rebif or offer an alternative? What are the proposed treatment options planned for CIS patients who are only eligible for the DMTs that will be withdrawn?

Role	Patient
Other role	Teacher
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:
I use plegridy - this means that I suffer fly like symptoms once every fortnight. I effectively lose a day out of every 14. I manage this by Injecting on a Sunday as this enables me to rest. If I had been forced to have Extavia instead I could suffer these side effects every other day thus making it impossible for me to work. For this reason I absolutely believe plegridy should remain available to patients with MS

Role	Patient
Other role	Bereavement Liaison Officer
Organisation	1969
Location	England
Conflict	n/a
Notes	

Comments on the ACD:
Currently take Copaxone & have have had no relapses.

Very short sighted decision based purely on cost, not benefit.

Very disappointed that a treatment I started very recently.

Role	Patient
Other role	Banker
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:
NHS England are again putting patients at risk by even contemplating this ridiculous idea. The costs of MS Sufferers being admitted to hospital every few weeks/months after relapsing will far outweigh the cost of the drugs and the potential further strain on hospital services as well as leaving people at risk of disability and death. You are playing Russian roulette with people lives. MS Patients are already denied treatment in England due the NHS England refusing to fund Savitex to help with neuropathic pain. Strange how the other UK health trusts fund this but England can't. Let's stop this selective process for health and wellbeing.

Role	NHS Professional
Other role	Consultant Neurologist

Organisation	Walton Centre Foundation Trust
Location	England
Conflict	No
Notes	

Comments on the ACD:
It is fair to say all the interferons are 'more alike than different' so making extavia the default and first line treatment makes sense economically. However it seems odd to lump Glatiramer (GA)in with this issue, as although it is similar efficacy to IFN, the side effect profile and mode of action is very different, so there are clearly going to be patients who for various reasons get on better with GA; removing this as an option seems illogical. You could also argue this for some of the IFNs which are significantly different in formulation eg Plegridy. Note an unintended consequence of this restriction would be an increase in use of oral first line DMT's, as well as extavia, eg aubagio and tecfidera, which are both MORE expensive than IFN & GA.

I assume the purpose of this exercise is to set up a negotiating position for the companies to reduce current list prices to the NHS, which is fair enough.

Role	Patient
Other role	Receptionist
Organisation	
Location	England
Conflict	n/a
Notes	

Comments on the ACD:
I have been on plegridy for over one year now I feel it has given

me my life back so far no relapse (I have RRMS) I am disgusted that you would consider this, there are bound to be other ways to save money on the NHS. This is a debilitating progressive disease which there is NO CURE as of yet. This is disgusting that you could do this to us all you wouldnt dream of taking the funding from drug addicts or people with alcohol issues or people who have never paid into the health service because some of which just couldnt be bothered get out of bed and actuall seek employment. You would never stop treatment for cancer patients so why MS patients. Why not stop people from other countries that just come specifically to use our FREE NHS why not crack down on that. Im begging please dont stop our treatments I for one want to be able to play with my grandchildren PLEASE reconsider . dont take this away from us.

Role	Patient
Other role	
Organisation	multiple sclerosis
Location	England

Conflict	No
Notes	

Comments on the ACD:
I just cannot understand why this is being proposed.It's playing god with people.What needs to be sorted is the ridiculously high prices the drug companies charge.Are you saying the neurologists that recommend them for patients don't know what they're doing.Surely it would have been flagged up before now if they weren't beneficial.You're penalising the wrong people who need it.People who have paid into the system all of their working life.Faceless people who don't have an inkling or a care about who this affects.Save money job done! People will end up having relapses then go back into hospitals putting yet more strain on our crippled NHS

Role	Patient
Other role	Computer Programmer
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:
I am a young woman, diagnosed 5 years ago with Rapidly Evolving RR MS.

I am currently taking DMD (Fingolimod). I am considering trying to become pregnant soon, and glatiramer acetate would have potentially been a drug I was looking into as recent evidence has been published which appears to suggest that it is safe to take during pregnancy.

1) Has all of the relevant evidence been taken into account?

I do not believe this paper has taken into account the recent evidence of the change in safety guidelines for glatiramer acetate in pregnancy and the recent change in EU legislation regarding its pregnancy category. To the best of my knowledge the paper does not properly evaluate the risks and benefits in pregnancy of glatiramer acetate vs other interferon - especially compared to the proposed alternative Extavia which is not recommended in pregnancy.

2) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I do not believe that the summary take account of the costs involved in higher risks to pregnancy and the cost to the NHS of managing MS in pregnancy and the cost of care to the neonate in the case of a relapse during the later stages of pregnancy. Including whether or not there could be greater risk of prematurity if the mother is unwell, and the cost to the NHS associated with that.

3) Are the recommendations sound and a suitable basis for guidance to the NHS?

I do not think the recommendations are sound and suitable guidance to the NHS for women of childbearing age wanting to become pregnant.

4) Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the

grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

YES

This guideline appears to discriminate against women of childbearing age, and against pregnancy and maternity.

I think the guideline could also be considered to be discriminatory against disability attributed to MS, by preventing a young women from enjoying the right to participate in creating a family (purely on the grounds of needing medication, and having to take something which is not suitable in pregnancy, when there is a pregnancy safe alternative available - glatiramer acetate) given that her peer, who is not disabled by MS, is able to enjoy this benefit. Creating a family has benefits to a women in other areas as well, often improving mental health, self esteem and giving purpose in life which results in reducing other costs to the NHS.

I believe it would be wrong for NICE to stop this treatment form being available.

Although I understand there are risks to any medication taken in pregnancy, with a more severe form of RR MS, stopping all DMDs, especially during pre-pregnancy and for the months is takes to conceive, could be disastrous for the long term health and outcome of the women.

I hope this is taken into consideration, even if copaxone was only licenced for women of childbearing age who might become pregnant.

Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:

It angers me that NICE would consider restricting access to any disease modifying therapy for newly diagnosed MS patients. As someone who was diagnosed just two years ago, I know the importance of having access to these drugs and being able to choose between them. I was put on Copaxone 18 months ago after careful consideration of all the side effects the drugs could cause (this consideration included Avonex (interferon beta-1a), Betaferon (interferon beta-1b), Plegridy (peginterferon beta-1a), Rebif (interferon beta-1a) in addition to Copaxone (glatiramer acetate). I chose Copaxone because it seemed it would interfere the least with my work as an orchestral musician and I have tolerated it well. It is essential that patients can choose from a list of appropriate medication or it will prevent them from leading normal, active lives.

I am also very concerned that NICE are restricting access to Copaxone when it is the one disease modifying therapy that has been proven safe to administer during

pregnancy. It highly discriminates against young women who may be considering having a family in the future. They must be granted access to this drug when they are initially diagnosed so that their options for motherhood are not limited and do no involve an unpleasant transition between medications. This proposal must not ever take effect!

Role	Public
Other role	Rec Consultant
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ACD: This propsal is very concerning due to the points below ; 1. the lack of choice for the patient 2. The impact on patient lifestyle, in particular those who work full time 3. the fact that the proposed drug cannot be guaranteed safe from viruses like CJD. Please consider these details when reviewing	

Role	Patient
Other role	Patient in MS
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ACD: I have had MS for 37 years. I have been taking Avonex since 1998 as this is proving successful for me. Writing as a patient, I would ask NICE to consider the importance of having the widest possible range of treatment options available for medical teams to discuss with their patients. Many of the MS appropriate treatments each only benefit a certain percentage of patients and therefore the widest range of availability is key. Otherwise it is discriminating against patients who may only benefit from one of the treatments being proposed for withdrawal.	

Role	NHS Professional
Other role	Doctor
Organisation	
Location	Scotland
Conflict	No
Notes	

Comments on the ACD:
As a medical practitioner but more in this case as a good friend of a MS sufferer it seems unhelpful to be so restrictive with treatment options. My friend needed to try a number of the agents examined until one suited him in terms of side effects that allowed him to continue to work full time. Patients and Doctors need choice not a one size fits all approach. As from life and clinical practice no two people or patients are the same. Different options often need to be tried to maximise someones quality of life.

Role	Patient
Other role	Teacher
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:
I do not understand the reasoning behind removing affective drug options for people with MS? Every patient is different and some are more tolerant to some medications than others. Also tolerances to side effects can change. So what happens when this side effects are too much for a patient? Should they just put up and be grateful for getting anything? Life with MS is hard and the future is uncertain. Having treatment options withdrawn for what appears to be financial reasons will end up costing more for care, hospital admissions, doctors appointment and inability to work, pay taxes etc. Please reconsider this desicion.

Role	Patient
Other role	
Organisation	
Location	N. Ireland
Conflict	No
Notes	

Comments on the ACD:
As a sufferer of relapsing remitting multiple sclerosis fortunate enough to have been prescribed plegridy I find this document an outrage. Though on their face the interferons appear to be the same, not all are suitable for the individual making the choice to take them as a first line therapy - and of all the interferons chosen by NICEas recommended, it would seem the most old fashioned and intrusive version of this therapy of all will be placed at the fore; it has to be mixed, risking needle stick injury, and then injected - not everyone is dextrous enough to accomplish this, fear of needles notwithstanding; it is intrusive - it has to be given 3 times a week compared with Plegridy and Avonex, given fortnightly. In short, it is a cheap, short sighted and dangerous therapy that is not always suitable for some patients.

The withdrawal of the interferons from frontline treatment seriously deprives those incapable of taking the stronger therapies offered deprives the new patient of choice. It is a sad day when, patients who read of therapies such as plegridy or avonex or even betaseron go to their neurologist in the knowledge that there are few other therapies in existence that will help them with this debilitating and crippling disease, knowing that they will not be able to get any further help. Is it fair and reasonable not only to deny the patient this choice, but to effectively tie the hands of neurologists

who have strived for years to build a satisfactory pharmacology that can be of help to their patients? Aret you determined to send neuroinflammatory care back to the dark ages, when nothing whatsoever could be done for sufferers?

The fight to obtain interferon as a therapy for MS was a long and hard one Please don't restart it in the name of cost effectiveness, when so many people - as yet undiagnosed - will come to rely on the choices among this group for their future wellbeing.

Role	NHS Professional
Other role	Consultant Neurologist
Organisation	UCLH
Location	England
Conflict	No
Notes	

Comments on the ACD:
We look after 3000 patients with multiple sclerosis at our Trust.

Copaxone is clearly required as it is the only DMT that has a licence (2017) to be administered in pregnancy and breast feeding. This does not apply to the beta-inteferons. MS is dominantly a younger female disease.

In our Trust we have no experience of Extavia. It has not been the preference of our patients with MS over the last decade.

It is surprising that there were no neurologists on the sub-panel which put this out to consultation

Role	NHS Professional
Other role	MS Pharmacist
Organisation	at The National Hospital for Neurology and Neurosurgery (UCLH trust)
Location	England
Conflict	No
Notes	

Comments on the ACD:
The different interferon devices and formulations available give the patients the opportunity to choose the one that fits better their lifestyle, increasing adherence.

Extavia® manual device is a SC preparation that has to be reconstituted. Many of our patients have problems with dexterity in their hands, so I dont think these patients are capable of doing this.

Not all the patients can tolerate all the interferon preparations. The adverse reactions are different in between the formulations; therefore by simplifying this to one preparation will eliminate treatment choice. Examples:

Eg 1: Extavia® is given alternative days, so some patients might not have enough

time to recover from flu-like symptoms or skin reactions in between doses.

A real patient example: I had a patient with low platelets with Plegridy but not with Avonex.

Another example: SC preparations and IM preparations do not have the same skin adverse reactions. For some patients this is not interchangeable.

Copaxone® is the only drug available for the treatment of RRMS that is not contraindicated in pregnancy and breastfeeding. When women are breastfeeding (after birth) is when they are at more risk of relapse.

Copaxone® is the only drug available for the treatment of RRMS which does not affect FBC, LFTs and U&Es. Copaxone® is very often prescribed when Tecfidera® or Fingolimod® is not an option due to lymphopenia.

For those patients that are needle phobic Extavia® manual device is not a choice, since the needle is exposed. Other preparations such as Plegridy® have the needle covered.

Rebismart® is an option for those patients that forget to take the medication or have careers, since the device has an alarm and tells you when the last dose was administer.

Role	Patient
Other role	Retired From Police Force On Ill-Health
Organisation	
Location	Wales
Conflict	No
Notes	

Comments on the ACD:

I am an RRMS sufferer diagnosed in 1991. I have been on Avonex since 2003/2004. It took me many years to get the drug, which back in the 90's was the drug to be taking in order to slow symptoms of the disease. I was completely incensed when I heard NICE were considering doing away with this and other Disease Modifying Drugs DMD's. I have not relapsed for the last 6 years and I believe Avonex has helped with this. People suffering with MS haven't chosen to have MS. It is a severely disabling disease, for which no two days are the same. An MSers life is seriously compromised. I have worked alongside a colleague, who has now passed away due to the effects of MS and know other people who have suffered as a result of having this awful disease.

My point is this:

a) Pharmaceutical Companies should not be allowed to continue selling these DMDs at such a high price. If they develop and market a new DMD that proves to be successful, then the cost of older products should be made cheaper

b) It's obvious that this is an NHS cost cutting exercise at the expense of over 100,000 people's welfare. I would like to know if NICE have viewed this proposal from this angle? An MSer is taken off one of the named DMD and given a cheaper

DMD. That MSer then relapses because that DMD wasnt so good. That MSer is seen by an MS Specialist Nurse and a Specialist and requires hospitalization for steroid treatment. This would then utilize a hospital bed and the varios nursing staff to monitor this patient. Steroid treatment is normally one week. I know - I've been through it a number of times!

Is Option b) cheaper than leaving an MSer on their current DMD that is working for them? Multiply this by the number of MSers currently taking one of the named DMDs in your proposal.

Your choice!!

Signed: A Very Unhappy MSer

Role	NHS Professional
Other role	Clinical Senior Lecturer and Honorary Consultant Neurologist
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:

I am extremely concerned that patient choice will be restricted to just one agent out of the interferons and glatiramer acetate. There is likely to be individual variation in the side effect profiles for each agent and this is not considered in the report. If the patient cannot tolerate Extavia then other options (IFN or GA) of similar efficacy cannot be considered if this appraisal is finally approved. This can only have a detrimental effect on patient care and choice.

Regarding Clinically Isolated Syndrome (CIS). This is still a very relevant sub-group which should be considered within the remit of the appraisal. The report states that " The diagnostic criteria will soon be revised again, which may mean that clinically isolated syndrome as currently defined will cease to exist." This is factually incorrect. The most recent guidelines (Thompson et al, Lancet Neurology, Dec 2017) still keeps clinically isolated syndrome as a distinct entity. If guidelines evolve and change every 1-2 years then when will the committee ever be able to consider clinically isolated syndromes?

The potentially earlier diagnosis of MS after a single clinical episode (CIS) raises another issue regarding the indication of Interferon Beta or Glatiramer Acetate. If MS is diagnosed in a CIS patient after cerebrospinal fluid oligoclonal band analysis or enhancing brain/cord lesions on magnetic resonance imaging, then what implications does this have on eligibility for first line injectables? If the diagnostic label changes to MS then do they need to have two attacks in two years to qualify? Whereas beforehand, if they were felt to have CIS with high risk of conversion to MS (e.g. on radiological grounds) they would qualify for Interferon-beta. So would they no longer qualify just because they have been diagnosed MS after a single relapse?

Role	Patient
Other role	Senior Software Developer
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:

I have relapsing remitting MS (first symptoms in 2010, diagnosed in 2012) and I have been taking Copaxone since 2013. I am very upset that Copaxone will no longer be available for newly diagnosed RR patients, whilst I understand that this will not affect my access to the drug it is beside the point. Copaxone has a different mechanism from the interferon-beta drugs and I don't understand why it has been appraised alongside them. Copaxone has minimal side affects and has allowed me to lead a full life. I have continued to work full time - I don't need to worry about flu like symptoms or taking medication which could potentially make me feel worse than my actual MS symptoms. Whilst I know Copaxone does not have any effect on disease progression whilst Extavia might, at the stage in my life when I was diagnosed (34 years old) I needed to have the confidence that I was taking a drug that I knew would not affect my fertility or my ability to work at a key point in my career but nevertheless would offer some mitigation against having a relapse. I have not experience any relapses since I began taking Copaxone and the minimal impact it has had my life has actually allowed me to often forget that I have MS.

I would ask NICE to reconsider this decision based on the fact that Copaxone does not produce flu like symptoms (and indeed any Copaxone side affects are minimal after the first year) and importantly it is also safe for women to take during pregnancy if necessary - neither of which is covered off by Extavia.

Role	Patient
Other role	Physicist
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:

Today, as a new patient, I began treatment with Avonex. I was astonished to be told by the training nurse of this NICE proposal, the adoption of which would seem incredibly harmful to the welfare of MS patients in England. One reason multiple Interferon-beta formulations are offered is that some patients react badly to particular formulations. A second reason is that patients can expect to develop some immunity to the treatment over time, necessitating a change of formulation. What can these patients do if only one formulation is offered, to which they react, or to which they develop antibody resistance? It leaves them without a treatment option, a ridiculous state of affairs when the medical community has worked hard over the years to broaden the available options to the current state.

Restricting treatment options will inevitably lead to a statistical average decline in health for MS patients, which will place a financial and logistical strain on hospital services that otherwise wouldn't be present. This proposal doesn't even make sense judged on the accountancy metric that seems to have inspired it.

Role	Patient
Other role	
Organisation	
Location	Scotland
Conflict	No
Notes	

Comments on the ACD:

I am sending you my comments on the recent report and recommendations of NICE on the use of interferons for MS patients.

First, some comments on the report itself. As an MS sufferer I find it somewhat difficult, if not offensive, to recognise the reports description of MS:

Symptoms can include pain, disturbance to muscle tone including weakness or spasticity, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment

This is a massive and quite unjust under-statement. 'Can include pain and disturbance to muscle tone - etc'! Last December we buried my Aunt who had spent the previous 15 years in a nursing home, totally bed bound and incontinent, and unable to be fed anything other than semi-liquid foods. Before entering the home, her husband (my uncle) had spent 10 years or more as a more or less full time carer. Similarly, an old friend of mine, in his early sixties, died of MS following a similarly traumatic experience of the disease.

Similarly later the reports states that:

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.

This too is a massive understatement and underestimation of the impact of MS on patients and carers. Perhaps I have been somewhat unlucky, but my Uncle, referred to above, fell into deep depression and committed suicide after years of trying to help my aunt, only to witness the unrelenting progress of MS.

MS sufferers might well question the NICE process and whether or not the process and associated panels were fully informed of the nature, impact and unrelenting progress of MS!

My other main point, however, is the report's more or less total absence of any

references to the side effects of the various interferon treatments.

I currently use Avonex (which I note will continue to be available to current users). I have been using Avonex for some 8 years or so and even now and with the use of Paracetamol and ibuprofen, I experience significant side effects in the form of a headache, general aches, fatigue and difficulty in concentrating on any one task or topic for more than 15 minutes or so. While the severity of these side effects varies from week to week they can last 24-36 hours, leaving me not able to do much for a day or so.

I notice that side effects from Extavia (to be injected every other day) are reported in terms that sound similar to Avonex. In the absence of any other information or reassurances from NICE that the side effects of Extavia do not last anything like as long as those from Avonex, then the recommendations concerning interferons could more or less restricting some future patients to an interferon treatment the side effects of which could leave some patients substantially impaired for most of the time.

I also wonder if and how the side effects were taken into account in the calculations of QALYs and urge NIE to provide information and explanations on this. I would also welcome confirmation from NICE that the side effects of Extavia are minimal in intensity and duration for all users, and will not impact on their working, family and personal life to any significant extent. Unless NICE can provide evidence of this then I am very much of the views that the recommendations concerning the use of Extavia and the removal of other interferons as DMDrugs for MS should be rejected

Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:
I believe the proposals by NICE will have appalling consequences for anyone suffering from the very complex effects of MS.

I was diagnosed in 2010 and it was a shock, I felt lost and I didnt know what to do. The MS Society, my MS Nurse and Neurologist not only educated and calmed me, but they gave me choice. Choice of how to deal with the diagnosis, choice of medication, choice of when I wanted to start and choice if I didnt feel comfortable with the medication I was taking etc. I didnt feel pressurised into taking one sort of medication or another and I felt in charge of when I would like to start medication and what I wanted to take. I can never fully explain how important that was, and still is, to me.
My MS nurse spent a long time going through all the options available and it right that I was able to make a choice that suited me best. I started taking Avonex and if I didnt feel comfortable with it or it had adverse effects, I would be able to change it until I found the right one. The proposal by NICE would take that away and that is fundamentally wrong.

An MS diagnosis is something that it incredibly difficult to deal with anyway and now having to worry that you dont have access to the medication that suits you the best or now being too scared to try another medication incase you would want to change back and cant, is something that will be devastating to many MS sufferers and yet to be diagnosed people.

Please give people the choice they deserve to get the medication thats right for them and for it not to become just another cost-cutting exercise and country lottery, which will have devastating consequences and far-reaching effects.

Thank you,

[redacted]

Role	Public
Other role	
Organisation	
Location	Other
Conflict	No
Notes	

Comments on the ACD:

[redacted]

24 January 2018

RE: Multiple sclerosis - interferon beta, glatiramer acetate (review TA32) [ID809]

I write in objection to proposed recommendation 1.2 in the National Institute for Health and Excellence (NICE) appraisal consultation document (issued December 2017) concerning beta interferons and glatiramer acetate for treating multiple sclerosis.

The recommendation states:

Glatiramer acetate, Avonex and Rebif (both interferon beta 1a), Betaferon (interferon beta 1b) and Plegridy (pegylated interferon beta 1a) are not recommended within their marketing authorisations as options for treating multiple sclerosis.

Implementation of this recommendation would result in an unacceptable reduction in the range of disease modifying treatments (DMTs) in the ˜moderate efficacy category available through the National Health Service (NHS) for new patients with MS (pwMS). For new patients, Extavia (interferon beta-1b) would be the only DMT in this

category available on the NHS.

According to the appraisal consultation document this recommendation has been proposed for reasons of cost-effectiveness on the basis that these treatments œwork similarly .

While the DMTs may œwork similarly , the efficacy, the related side effects and the lifestyle impact of the consumption regimes of each of these drugs vary considerably. It is critical that pwMS have choice of treatment options, particularly given the wide range of symptoms pwMS can experience and that patients tolerance for risks in treatment is varied.

Side effects are widely recognised as a barrier to effective treatment. Preventing pwMS from selecting which DMT works best for them vis a vis side effects will have a measurable negative impact on the management of MS in the United Kingdom. Currently, the UK has one of the lowest prescribing rates for MS DMTs in Europe and it is gravely concerning that rates would likely fall further as a consequence of a reduction of patient choice such as the one proposed in the NICE appraisal consultation document.

It also concerning that the NHS could fall further behind the standard of best practice operating in comparable jurisdictions. It is noted that all the DMTs the recommendation proposes removing from the NHS are available to pwMS in Australia under the General Schedule of the Australian Governments Pharmaceutical Benefits Scheme. (con't)
(con't) The views of key stakeholder organisations on the issue of diverse treatment options are clear.

The Multiple Sclerosis Society UK has advised diversity œwill 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 and œDiversity 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.

The Multiple Sclerosis Trust, meanwhile, argues œShared 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 .

While the cost effectiveness of treatments must be a consideration in the delivery of a sustainable NHS, it is paramount that the NHS continue to provide patients with treatment options.

The reduction of DMTs in the moderate efficacy category from six to one is unacceptable and not in the best interests of pwMS. While all the DMTs should be retained on the NHS for new patients, there should at least be a minimum of three available to patients.

I urge the appraisal committee to recognise the importance of patient choice at its fourth meeting on 6 March and remove (or revise) recommendation 1.2 in the final

version of the document.

Yours sincerely,

[redacted]

Citations:

Avonex (https://www.pbs.gov.au/pbs/search?term=avonex);

Betaferon (https://www.pbs.gov.au/pbs/search?term=betaferon);

Copaxone (https://www.pbs.gov.au/pbs/search?term=copaxone);

Plegridy (https://www.pbs.gov.au/pbs/search?term=Plegridy);

Rebif (https://www.pbs.gov.au/pbs/search?term=rebif).

Multiple Sclerosis Society UK submission to National Institute for Health and Excellence review TA32, p3

Multiple Sclerosis Society UK submission to National Institute for Health and Excellence review TA32, p18

Multiple Sclerosis Trust UK submission to National Institute for Health and Excellence review TA32, p6

Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:
As the people who this decision will impact on have not been diagnosed yet, how have they been consulted?

I see that two MS charities have been consulted, however there are other organisations and web forums that could reach this groups of people as well as those that are newly diagnosed.

The timing (just before Christmas) and short length of this consultation suggests that there is not the appetite to fully consult with potential and current patients.

I would expect this to be challenged if I ran a consultation in this way in the (NHS) organisation that I work for. At the very least, it is poor practice.

I was diagnosed with MS in 2016. With the support of my consultant I chose to go on glatiramer acetate. I chose this over the beta interferons as a first line treatment

mainly because I work full time and didn't think I would be able to continue doing this if I was also dealing with flu like side effects. This has worked well for me so far. My main MS symptom is fatigue so I am able to continue working full time with some home working as an adjustment.

There is a potential economic impact of this proposal. While the treatments may have the same efficacy, the savings gained by offering only the cheapest could have an adverse economic and social impact on patients personally as well as their ability to contribute as taxpayers.

Different people tolerate different treatments differently.

There is a real risk with this that someone not tolerating extavia will be left without an alternative. As well as having potentially devastating consequences for the individual and their family, this will almost inevitably lead to extra costs for the taxpayer in terms of medication to manage symptoms such as pain and social and healthcare costs as a result of disability.

After diagnosis I engaged with other people with MS for support and almost everyone I've met has switched treatments at some point either as a step up or simply because they couldn't tolerate the side effects of the treatment they were on.

I have one friend who started on one of the interferons about seven years ago. He couldn't cope with the sickness this caused as a side effect, came off it after a few weeks and decided that the experience was bad that he wouldn't try anything else. That was his choice but, without an alternative, people trying extavia who have a bad experience will be left in the same position without anything unless they presumably quality for one of the stronger treatments (a route I personally wouldn't want to go down unless I believed it was the bast thing clinically because my MS was getting much worse). My friend has problems with mobility, fatigue and is now blind. Of course that may have happened anyway. There is still a direct cost to the NHS because he takes medication to help with pain and mobility.

In addition, alternatives will be available to people who can afford it so this decision will only impact on people who can't afford to pay for their medication privately.

One size doesn't fit all and there is a real risk this decision will leave many people with MS without treatment at all.

Role	NHS Professional
Other role	Clinical Reader and Hon Consultant Neurologist
Organisation	
Location	Scotland
Conflict	No
Notes	Was clinical advisor to Warwick assessment group

Comments on the ACD:
Glatiramer may well become cost-effective once the generic version becomes available, which has been shown to have similar efficacy to the Teva product. Teva have been trying to block its use. It would be a shame if this was not addressed in this document as if generic glatiramer becomes available this recommendation will immediately become obsolete.

I think comparing IFN and glat with best medical Rx and not newer 1st line drugs with same indication (dimethyl fumarate, teriflunomide) makes this guideline much less useful clinically and has generated an odd recommendation. All the 1st line drugs have similar efficacy but the newer oral agents are much more expensive (without any discount) than any of the existing IFNs and glat. It seems paradoxical therefore, that both the newer oral agents are approved for use and yet only Extavia of the older drugs will be recommended. Moreover, the older injectables have a much longer safety record (including during pregnancy for some) and do not carry the risk of PML so some pts who fail Extavia (eg for side-effects) may wish to try another interferon or glatiramer before thinking of using a newer oral agent. This would probably be a more cost-effective approach. So it is counter-intuitive that this NICE recommendation will prevent clinicians offering that option.

Role	NHS Professional
Other role	
Organisation	
Location	England
Conflict	Yes
Notes	I have been providing occasional consultancies services for Novartis, Biogen, Teva, Roche, Genzyme.

Comments on the ACD:

This recommendation will imply that we do not have any treatment that can be used in pregnancy. The contraindication against the use of Copaxone in pregnancy has been removed from the updated SmPC. Copaxone is the only medication which is NOT contraindicated in pregnancy. It is true that the SmPC states that it it preferable to avoid Copaxone in pregnancy but it adds "unless the benefit to the mother outweighs the risk to the foetus". There are many individual cases where this happens. So what does a woman with active multiple sclerosis who is pregnant supposed to do if she cannot use Copaxone?

The revised McDonald criteria for the diagnosis of MS have been published. The definition of clinically isolated syndrome has not changed and this condition has not ceased to exist.

Clinically isolated syndrome represents (in most cases) an early stage of MS which one relapse is seen. CIS requires treatment, however treatments that are licensed for people with MS and two relapses in the previous two years are not indicated. Therefore, if a patient has MS but one relapse and active MRI scan what is he/she supposed to do?

Extavia preparation means an injection every other day. Injections are associated with flu-like symptoms, and reactions at the site of injections. The appraisal consultation document does not consider that having side effects every other day is different from having side effect once every two weeks (Plegridy), once a week (Avonex) and even three times a week (Rebif).

This recommendation will imply that patients cannot choose the medications which give less frequent post-injection reactions. None of my patients (20 years of practice in the MS service) has ever chosen Extavia.

When the fever after the injections is high and the side effects are serious, patients do not go to work, and this is a loss of productivity and additional costs to the society.

It seems that these costs are not considered in the cost-effectiveness calculation.

The following statement in section 3.4: "A single demyelinating event is known as clinically isolated syndrome (CIS), and people experiencing this have a high chance of developing multiple sclerosis" is incorrect, as patients with CIS may have already MS if they fulfil the McDonald criteria for MS (Thompson AJ, The Lancet of Neurology 2017). This should be corrected.

The appraisal recognises that some drugs cause more side effects than others, but then it comments on "the size of the confidence intervals", thereby dismissing the significance of the findings.

On a personal and societal level, less severe and less frequent side effect are associated with better quality of life, longer time spent in employment and education, which, in turn, it is expected to reduce the indirect costs of MS.

The consultation documents concludes that glatiramer acetate, Avonex, Betaferon, Plegridy and Rebif were not cost effective at current prices.

Is it possible to negotiate a lower price for these drugs rather than stopping patients to go on them?

I agree that these technologies are not considered innovative anymore, but patients continue to choose them. This is because there are very long-term data (more than 20 years) about these drugs which are substantially safe.

All new technologies, which are more innovative, carry much higher risks of serious side effects and their long-term safety data are unknown.

Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Dear Sir or Madam

I have just been made aware of the current consultation taking place on the use of Interferon treatments. I am not sure whether you are taking comments from members of the public and I have been unable to find a designated response site. However I feel it most important to report my views and would therefore be grateful if this e-mail could be forwarded to the appropriate team.

I have had MS since 2001 and commenced on Rebif some years later. As you can imagine starting on thrice weekly injections is a very daunting prospect and even now I find it very difficult. However I have no doubt that the medication has delayed the deterioration of my symptoms preventing further reliance on medical and social care. It also enabled me to continue working for the NHS full time as a Health Visitor until I retired four years ago (not for health reasons).

I appreciate that the NHS has serious financial considerations which need to be addressed but denying other patients the opportunity to be prescribed this proven medication is very concerning. There is very little available for MS patients.

I understand that the recommendation includes that the prescribing of Rebif can be continued until a mutual agreement between Consultant and patient is reached. My concern is that pressure will be put on Consultants to stop the use of Rebif even for existing patients.

Life with MS is one of total uncertainty but the use of disease modifying therapies helps a little to continue with as normal life as possible. I am therefore opposed to reducing the choice of therapies available.

Yours faithfully

[redacted]

Role	NHS Professional
Other role	consultant neurologist
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:
I am a consultant neurologist in the Multiple Sclerosis service at University College London Hospitals NHS Foundation Trust, but my response represents my individual opinion and has not been reviewed by the trust.
I am concerned that the only evidence which has been considered is efficacy and cost, and that no evidence has been reviewed regarding side-effects, tolerability or safety in pregnancy.

I am concerned that no evidence has been reviewed regarding the pharmacological and clinical differences between the beta interferons and glatiramer acetate. Although the efficacy of the beta interferons and glatiramer acetate are similar, they are completely different classes of drugs with different modes of action and contraindications. For example, beta interferons, including Extavia, are contraindicated in patients with severe depression, but glatiramer acetate is not contraindicated. Depression is common in multiple sclerosis, and so this recommendation means that patients with severe depression will not have the option to be treated with a safe injectable therapy.

I am concerned that no evidence has been reviewed regarding differences in side-effects between the beta interferons and glatiramer acetate. For example, beta interferons commonly cause liver enzyme rises, or more serious hepatotoxicity, but glatiramer acetate does not cause significant hepatotoxicity. It is quite common that a patient has to stop beta interferon due to a liver enzyme rise, and for the patient to be then switched to glatiramer acetate. Beta interferons are also contraindicated in patients with significant liver disease, and so glatiramer acetate is the only safe injectable therapy for these patients.

I am concerned that no evidence has been reviewed regarding the frequency of administration, and associated tolerability of the different preparations of beta interferon and glatiramer acetate. Extavia is administered subcutaneously on alternate days. There are many patients who find injections very difficult to tolerate, either physically or psychologically, and are unable to adhere to such a frequent administration regime. In these patients, a once a week (Avonex) or once a fortnight (Plegridy) injection is much easier to tolerate and improves adherence (and so efficacy). Beta interferons may also frequently cause post-dose flu-like reactions, which may impair function or be disabling, in which case a less frequently administered preparation is better tolerated. For example, it is common scenario that a patient who is working who suffers flu-like reactions may just choose to inject once a week at the weekend so that the flu-like reaction does not interfere with work.

I am concerned that the evidence regarding the safety of the different drugs in pregnancy has not been adequately reviewed. There has been sufficient data to indicate no malformative or feto/neonatal toxicity of Copaxone for the marketing authorisation to be changed so that it is no longer contraindicated in pregnancy. This has resulted in many women choosing to take Copaxone while trying to conceive and, if the risks are felt to outweigh the benefits, to even continue on treatment during pregnancy. As it may take up to several months or years to conceive, if women do not have the option of taking Copaxone, they are at increased risk of relapse and disability while not on treatment. This recommendation has not reviewed this evidence, but has just considered one part of the sentence in the marketing authorisation which says “it is preferable to avoid the use of Copaxone during pregnancy” but ignores the part of the sentence which says “unless the benefit to the mother outweighs the risk to the foetus”, which may be felt to be the case, and that this is just a “precautionary measure”. Extavia is contraindicated in pregnancy and so, unless this recommendation is implying that Extavia should be prescribed outside the marketing authorisation, this means that women who are trying to conceive cannot be treated and are put at greater risk of relapse. The available data on Extavia in pregnancy indicates that there may be an increased risk of spontaneous abortion, and so most women would choose to stop Extavia before trying to conceive. The recommendation that Extavia is the only option is discriminatory against women.

I am concerned that this recommendation which concerns the clinical welfare of people with multiple sclerosis was made by a committee which did not include a single member who has clinical experience of treating multiple sclerosis, such as a neurologist, MS nurse specialist or MS pharmacist.

I am concerned that this recommendation is inequitable and does not take into account individual differences in the tolerability or safety of these drugs and is discriminatory against people with multiple sclerosis.

Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence: Addendum 8

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/

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1 Introduction to this addendum

This addendum aims to address recent comments from manufacturers, especially as regards what is feasible and not feasible for further modelling; appraise new economic evidence submitted; and submit economic analyses accounting for new evidence.

These new economic analyses implement new discounts where applicable, including for Brabio, a generic form of glatiramer acetate, and explore data from related technology appraisals to inform a revised mortality assumption. In addition, we offer analyses that more directly account for discontinuation of treatment in advanced EDSS scores.

2 Response to consultees: general issues raised

2.1 Accounting for drug-specific waning, adverse events, route of injecting and disutilities, and infrastructural contributions

A common thread running through multiple submissions is the possibility of drug-specific modelling of adverse events, discontinuation rates, and preferences relating to route and frequency of injection. In an ideal scenario, modellers would have clear information relating to each of these issues, as well as information that was internally consistent in respect of source quality. This is not the case in this appraisal. For example, while the appraisal committee preferred the AG NMA for modelling comparative effectiveness, they preferred data from the risk sharing scheme (RSS) for economic modelling. There are pros and cons to each of these sources of data which have been discussed in details at previous appraisal committee meetings. One implication of the use of RSS data was the decision to use the empirically derived 5% discontinuation rate. As part of our analyses using drug-specific NMA estimates, we included discontinuation estimates derived from the clinical trials. These were not preferred for reasons previously discussed by the appraisal committee.

In addition, Biogen requested that we undertake an analysis for drug-specific waning. We do not have access to the individual participant data needed to undertake this analysis.

We note that in order to account for the diversity of issues raised by company submissions, we would need to draw evidence on relating to clinical effectiveness from several different sources, possibly also resorting to evidence from our network meta-analysis. In addition, modelling the consequences for adherence (and thus treatment effect) that for example decreased injection frequency would

represent would require an extensive amount of work, and tenuous methodological assumptions, to incorporate possible benefits of one non-RSS drug (pegylated IFN β-1a, or Plegridy): however, this evidence does not exist. Intuitively, benefits or disbenefits of injection frequency would already have been captured by the RSS for on-scheme drugs (e.g. IM IFN β-1a (Avonex)).

Finally, it would appear that a key thread throughout the company submissions is the value of patient choice and of infrastructural contributions from companies. It is not for us to comment on the value of patient choice but we note that this would be nearly impossible to operationalise in the context of the cost-effectiveness model. We accounted for infrastructural contributions in early addenda, before these were set aside by the appraisal committee.

2.2 Class effects, including in respect of pegylated IFN β-1a (Plegridy)

We note Teva's and Merck's comments on the limitations of using class estimates of effectiveness, and Biogen's comments in respect of the limitations of extending a class effect to Plegridy. We have discussed in previous addenda the different options for inclusion of Plegridy, and the limitations of these options. In addition, we have also provided drug-specific ICERs using the RSS data.

In support of their assertion that a class effect is not appropriate for Plegridy, Biogen cite the NMA, non-comparative evidence for longitudinal extensions of the original ADVANCE trial, and two matching indirect adjusted comparisons although we were not provided with these presentation posters. While we accept Biogen's point that the NMA showed favourable results for Plegridy, it should be noted that 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. Indeed, the basis for setting aside the NMA evidence was that the RCT evidence appeared at consistently high risk of bias (mainly because of the risk of unblinding of participants) and their short-term nature did not provide confidence in their value, in terms of outcomes measurement especially as compared to the RSS. The non-comparative longitudinal extensions are not in themselves persuasive since they do not establish the effectiveness of Plegridy relative to other options. Finally, the matched adjusted indirect comparisons presented by Coyle et al [1] and Scott et al [2]are only available in abstract form. While these might certainly be of use in estimating a possible difference in effectiveness between Plegridy and other drugs, the evidence from abstracts alone does not provide sufficient basis for a full formal appraisal. However, the key issue with this evidence remains the same as with the larger body of clinical trial evidence: 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. In fact, the inclusion of matching indirect comparisons as an observational analysis could be seen to compound the two different set of biases inherent in clinical trial and observational data.

We would like to remind the committee that, compared to other interferon beta-1a formulations, Plegridy or peginterferon beta-1a is an interferon beta-1a conjugated to a methoxy polyethylene glycol molecule. The presence of this conjugated molecule affects the duration of the pharmacodynamic response to peginterferon beta-1a which is more sustained and prolonged compared to non-pegylated interferon beta-1a, allowing a reduced frequency of administration, however this does not provide a rationale to support a greater effectiveness of peginterferon beta-1a compared to a non-pegylated formulation.

The decision by the appraisal committee to consider a class effect including Plegridy is consistent with decisions made by other HTA bodies. For example, the French HTA body concluded that Plegridy does not provide clinical added value (ASMR V) meaning that Plegridy was deemed not to show any additional clinical benefit compared with available therapies (Transparency Committee opinion April 2015).

2.3 Selection bias

We acknowledge Teva's observation regarding selection bias as an objection to pooling estimates. We note that both we and the Department of Health have noted that selection bias presents a strong source of bias that must be considered when calculating ICERs using the RSS data. We note the broader justification for pooling however as raised by the committee, that is, a clinical interpretation of the evidence suggesting that the interferons are broadly exchangeable.

3 Response to consultees: implications for modelling

3.1 Availability of newer, higher-quality mortality evidence

In the previous appraisal committee meeting, pairwise ICERs incorporating mortality estimates from Pokorski et al [3]were presented. It was agreed at the meeting that this source of mortality evidence was unpersuasive and of low quality. Subsequently, mortality evidence from a study by Jick and colleagues (2014) [4], used in the appraisal of cladribine (ID64), has been presented to us. This evidence is considerably more contemporaneous than evidence from Pokorski et al, and relies on data from the UK General Practice Research Database. This evidence covers both pre and post RSS implementation periods (1993 to 2006). It includes 1,822 MS cases matched to 18,211 controls and

provides a stronger basis for implementation of a differential mortality assumption than Pokorski et al[3].

A potential issue, however, relates to the choice of mortality multiplier. In Table 5 of Jick et al. (2014), hazard ratios are presented for males vs females, RRMS (incorporating secondary progressive MS patients) vs PPMS, and overall. In this addendum, we have chosen to implement the fully adjusted hazard ratio for RRMS (HR=1.50) as we believe this matches the risk sharing scheme population better than would be achieved by attempting to reweight male and female hazard ratios. We need to exclude patients with PPMS who are outside the scope of this appraisal. We used a conservative approach in choosing the HR estimate adjusted for all possible covariates. We consider this more accurately reflects differences in mortality than the RRMS adjusted estimate (HR=1.94). We implemented this new estimate for EDSS states 0-9, thus avoiding the double-counting problem with the previous mortality multiplier.

3.2 Costs of treatment at EDSS state 7 and beyond

In their submission, Teva note that treatment costs continue in EDSS states 7, 8 and 9. We do not regard this as an error but as an attempt to model the reality of clinical practice. Indeed, 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 to reasonable evidence based care pathway where drugs are used within the scope of their indications. We therefore present analyses of the base case with treatment discontinuation at EDSS stages 7, 8 and 9.

3.3 Analysis of risk sharing scheme data incorporating treatment switching

Teva suggest that the analysis of RSS data incorporate treatment switching. However, we note that we do not have access to individual patient data from the risk sharing scheme. Second, we agree with Teva in principle that an analysis which includes patients who switch treatments (as these were excluded from the original risk sharing scheme estimates) would be appropriate. Unfortunately, we only have access to treatment switching data for Teva and therefore have not been able to replicate comparative treatment switching analyses in this respect.

4 Validation of companies' analyses

In this section, we present a validation of results presented by Biogen and Teva, respectively.

4.1 Biogen's analyses

- IM IFN β-1a 30 µg (Avonex)

Scenario analyses:

1. *Base case (current committee preferred assumptions)*
2. *Base case with no additional waning at year 10+*
3. *Base case with pooled HR excluding data after patients switch to any other DMT (variant c1b, slide 14, AC meeting 3)*
4. *Individual RSS CDP HR for IM IFN β-1a 30 µg*
5. *Meta-analysis pooled CDP HR + waning aligned with more recent TAs (i.e. 25% at year 2+, 50% at year 5+)*
6. *Meta-analysis individual treatment effect (ARR, CDP6M) + waning aligned with more recent TAs + Avonex specific annual discontinuation rate (9.9%)*
7. *Meta-analysis individual treatment effect (ARR, CDP3M) + waning aligned with more recent TAs + Avonex specific annual discontinuation rate (9.9%)*

Table 1: Scenario analyses for IM IFN β-1a 30 µg (Avonex), using list price

Scenario	Biogen			Assessment group		
	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY gained)	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY gained)
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]			
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2: Scenario analyses for IM IFN β-1a 30 µg (Avonex), using discounted price

Scenario	Biogen			Assessment group		
	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY gained)	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY gained)
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]			
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- SC pegylated IFN β-1a 125 µg (Plegridy)

Scenario analyses:

1. *Base case (current committee preferred assumptions)*
2. *Base case with no additional waning at year 10+*
3. *Base case with pooled HR excluding data after patients switch to any other DMT (variant c1b, slide 14, AC meeting 3)*
4. *N/A – Plegridy not included in the RSS*
5. *Meta-analysis pooled CDP HR + waning (25% at year 2+, 50% at year 5+) aligned with more recent TAs*
6. *Meta-analysis individual treatment effect (ARR, CDP6M) + waning aligned with more recent TAs+ Plegridy specific annual discontinuation rate (10.4%)*
7. *Meta-analysis individual treatment effect (ARR, CDP3M) + waning aligned with more recent TAs + Plegridy specific annual discontinuation rate (10.4%)*

Table 3: Scenario analyses for SC pegylated IFN β-1a 125 µg (Plegridy), using list price

Scenario	Biogen			Assessment group		
	Incremental Costs (£)	**Incremental QALYs**	**ICER (£/QALY gained)**	**Incremental Costs (£)**	**Incremental QALYs**	**ICER (£/QALY gained)**
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	-	-	-	-	-	-
5	[redacted]	[redacted]	[redacted]			
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4: Scenario analyses for SC pegylated IFN β-1a 125 µg (Plegridy), using discounted price

Scenario	Biogen			Assessment group		
	Incremental Costs (£)	**Incremental QALYs**	**ICER (£/QALY gained)**	**Incremental Costs (£)**	**Incremental QALYs**	**ICER (£/QALY gained)**
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	-	-	-	-	-	-
5	[redacted]	[redacted]	[redacted]			
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In summary, we validated/replicated the majority of these scenario analyses as provided by Biogen. For scenario analysis 5 for IM IFN β-1a 30 µg (Avonex), the AG were unable to decipher the result of

the '*meta-analysis pooled CDP HR*'; hence we were unable to validate this result. Additionally, the AG noted that the estimated mean incremental QALYs for scenario 7 were not the same and, given that the only change made to this analysis was a discount on list price, we would expect both scenarios to have the same incremental QALYs with different incremental costs. Similar discrepancies were seen in Biogen's results (estimated mean incremental QALYs) for scenarios 6 and 7 for SC pegylated IFN β-1a 125 µg (Plegridy).

4.2 Teva's analyses

- Switching to other RSS DMTs and to non-Scheme DMTs

Table 5: Glatiramer acetate 20 mg SC once daily/40 mg SC three times weekly (Copaxone)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	228,038	-	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					

- Accounted for the treatment costing structure identified by Teva (excluding treatment costs in EDSS 7, 8 and 9)

Table 6: Glatiramer acetate 20 mg SC once daily/40 mg SC three times weekly (Copaxone)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	228,038	-	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					

- Using Teva's assumptions
    - Incorporating PAS price for Copaxone
    - Hazard ratio based on Copaxone-specific RSS data for patients who switched treatment
    - Treatment costs removed for people in EDSS 7, 8 or 9 health states

Table 7: Glatiramer acetate 20 mg SC once daily/40 mg SC three times weekly (Copaxone)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	228,038	-	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					

In summary, the AG validated/replicated the analyses and results provided by Teva.

5 AG analyses for RRMS, committee preferred assumptions, and discounts

In this section, we present our analyses (using pooled / individual estimates; using AG/Jick method for mortality) for RRMS using the committee's preferred assumptions, accounting for the treatment costing structure identified by Teva and, where appropriate, discounts.

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 discounted prices for each drug;
- including carers' disutilities;

Table 8: Discount prices provided by NICE

Drug	List price	Discounted price	Annualisation factor (of 365.25 days/year)	Annualised price
IFN β-1a 30µg IM once weekly (Avonex)	£651.76	[redacted]	13.04	[redacted]
IFN β-1b 250 µg every other day (Betaferon)	£596.63	[redacted]	-	-
20 mg SC once daily (Brabio)	£462.56	[redacted]	13.04	[redacted]
Glatiramer acetate 20 mg SC daily (Copaxone)	£513.95	[redacted]	13.04	[redacted]
IFN β-1b 250 µg every other day (Extavia)	£596.63	[redacted]	12.18	[redacted]
IFN β-1a 22 µg SC three times a week (Rebif)	£613.52	[redacted]	13.04	[redacted]
IFN β-1a 44 µg SC three times a week (Rebif)	£813.21	[redacted]	13.04	[redacted]
Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)	£651.76	[redacted]	13.04	[redacted]

5.1 Pooled analyses with AG mortality (AG preferred analyses)

In sections 5.1 and 5.2, we report the results of the pairwise analyses using pooled estimates of implied hazard ratio and annualized relapse rates against individual drug discounted costs and individual estimates, respectively. Results are presented below (see Table 9 through Table 23).

Table 9: IFN β-1a 30µg IM once weekly (Avonex)

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 10: IFN β-1b 250 µg every other day (Betaferon)

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 11: Glatiramer acetate 20 mg SC once daily (Brabio), using list price

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	228,000	-	7.148	-	-
20 mg SC once daily (Brabio)	258,900	30,900	8.047	0.899	34,400
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 12: Glatiramer acetate 20 mg SC once daily (Brabio), using interim price

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	228,000	-	7.148	-	-
20 mg SC once daily (Brabio)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 13: Glatiramer acetate 20 mg SC once daily/40 mg SC three times weekly (Copaxone)

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 14: IFN β-1b 250 µg every other day (Extavia)

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 15: IFN β-1a 44/22 µg SC three times a week (Rebif)

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					

Table 16: Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)

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)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

5.2 Individual analyses with AG mortality

Table 17: IFN β-1a 30µg IM once weekly (Avonex)

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 18: IFN β-1b 250 µg every other day (Betaferon)

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 19: Glatiramer acetate 20 mg SC once daily (Brabio), using list price

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	228,000	-	7.148	-	-
20 mg SC once daily (Brabio)	255,400	27,400	8.245	1.097	25,000
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 20: Glatiramer acetate 20 mg SC once daily (Brabio), using interim price

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	228,000	-	7.148	-	-
20 mg SC once daily (Brabio)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 21: Glatiramer acetate 20 mg SC once daily/40 mg SC three times weekly (Copaxone)

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 22: IFN β-1b 250 µg every other day (Extavia)

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 23: IFN β-1a 44/22 µg SC three times a week (Rebif)

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					

5.3 Implementing the mortality multiplier reported in the Jick's study

Mortality multiplier used in TA441. *In its original appraisal of the RSS model, we 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'. We 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, we think that this modification to the assumptions could be of interest to the committee's decision-making. We welcome Merck's attempt to implement this mortality multiplier functionality within the model. On inspection of the model (and transition matrices), we note that there is an increased risk of progression from EDSS 0-8 to progressing to EDSS10, but a reduction in the risk of death from EDSS 9 to 10. Additionally, there were no risks associated with background mortality. The results of Merck's implementation of Pokorski's mortality multipliers are presented in Table 24.

Table 24: IFN β-1a 44/22 µg SC three times a week (Rebif), using Porkorski's mortality multipliers

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	240,000	-	6.902	-	-
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					

These results showed that there is a decrease in expected mean QALYs for both BSC and IFN β-1a 44/22 µg SC three times a week (Rebif), but an increase in expected mean costs for both treatment options. These results may be explained by the reduction in the risk of mortality from EDSS 9 to 10, thus more people remaining in EDSS 9 state and incurring higher health state costs.

Jick and colleagues reported a hazard ratio of 1.50 (95%CI: 1.06, 2.14), suggesting that people living with RRMS have a 1.5-fold increased risk of all-cause mortality compared with the general population across all EDSS levels.
Applying the mortality estimates from the Jick et al paper, the AG is concerned about the clinical plausibility of transition probabilities from EDSS states 0-9 to EDSS state 10 (death state).
Indeed, using the AG method for mortality, the transition matrix from EDSS state 0-9 to EDSS 10 provided below on Table 25 shows there is no transition to EDSS state 10 from EDSS states 0-6 but only from EDSS states 7, 8, and 9. Moreover, it shows that transition to death is higher from EDSS 9 (23.87%) compared to EDSS 7 (<0.1%) which is consistent with the growing severity of the disease. This table was obtained applying a pooled effect estimate for relapse rate and confirmed disability progression but individual effect estimates for these two outcomes would provide a similar trend.

Table 25: One-year transition matrix for age of onset below median (using AG method)

		From EDSS state									
		0	1	2	3	4	5	6	7	8	9
To EDSS state	0	0.6870	0.0612	0.0169	0.0062	0.0018	0.0005	0.0001	0.0000	0.0000	0.0000
	1	0.2110	0.6787	0.1265	0.0522	0.0225	0.0056	0.0014	0.0002	0.0000	0.0000
	…	…	…	…	…	…	…	…	…	…	…
	9	0.0000	0.0000	0.0000	0.0004	0.0007	0.0014	0.0052	0.0189	0.0608	0.6252
	10	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001	0.0077	0.2387

Applying the Jick method for mortality, the transition matrix from EDSS state 0-9 to EDSS 10 is provided on Table 26.

Unlike the previous transition matrix, there are transitions to EDSS state 10 (death state) from any EDSS state between 0 and 9. Most importantly, the probability to transition to EDSS 10 is constant at a probability of approximately 0.065 across each EDSS state. In other words, the probability to transition to EDSS 10 (death state) is the same for patients with EDSS state of 0 and those with EDSS state of 9. Therefore, the AG believe that the pathway implied by the use of the Jick method is clinically implausible.

Table 26: One-year transition matrix for age of onset below median (based on Merck's method)

		From EDSS state									
		0	1	2	3	4	5	6	7	8	9
To EDSS state	0	0.64244	0.05725	0.01582	0.00580	0.00164	0.00051	0.00012	0.00001	0.00000	0.00000
	1	0.19735	0.63464	0.11833	0.04877	0.02105	0.00526	0.00132	0.00015	0.00001	0.00000
	…	…	…	…	…	…	…	…	…	…	…
	9	0.00000	0.00001	0.00004	0.00033	0.00062	0.00134	0.00491	0.01772	0.05727	0.76797
	10	0.06487	0.06487	0.06487	0.06487	0.06487	0.06487	0.06487	0.06487	0.06487	0.06487

In summary, to reflect an increase in mortality in the model for people living with MS would require a hazard ratio that represents non-MS related mortality applied to the general population mortality, in addition to MS-related mortality as seen in the British Columbia MS cohort. In the absence of such estimates, we believe the use of the Merck's method based on Jick's mortality multiplier is not clinical plausible. In sections 5.4 and 5.5, we have provided the ICER estimates using the Jick method for completeness.

5.4 Pooled analyses with Jick's mortality multipliers

In this section, we report pairwise analyses using pooled estimates of implied hazard ratio and annualized relapse rates against individual drug discounted costs (Table 27 through Table 34), using Jick and colleagues and proposed by Merck.

Table 27: IFN β-1a 30µg IM once weekly (Avonex)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	267,900	-	6.924	-	-
IFN β-1a 30µg IM once weekly (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 28: 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	267,900	-	6.924	-	-
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 29: Glatiramer acetate 20 mg SC once daily (Brabio), using list price

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	267,900	-	6.924	-	-
20 mg SC once daily (Brabio)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 30: Glatiramer acetate 20 mg SC once daily (Brabio), using interim price

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	267,900	-	6.924	-	-
20 mg SC once daily (Brabio)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 31: Glatiramer acetate 20 mg SC once daily/40 mg SC three times weekly (Copaxone)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	267,900	-	6.924	-	-

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-1b 250 µg every other day (Extavia)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	267,900	-	6.924	-	-
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 33: IFN β-1a 44/22 µg SC three times a week (Rebif)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	267,900	-	6.924	-	-
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 34: Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	267,900	-	6.924	-	-
Pegylated IFN β-1a 125 µg SC every two weeks (Plegridy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

5.5 Individual analyses with Jick's mortality multipliers

Finally, we report the results of the pairwise analyses using individual estimates of implied hazard ratio and annualized relapse rates against individual drug discounted costs. Results are presented below (see Table 35 through Table 41). These analyses use the method proposed by Merck to implement the mortality multiplier reported by Jick and colleagues.

Table 35: IFN β-1a 30µg IM once weekly (Avonex)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	267,924	-	6.924	-	-

IFN β-1a 30µg IM once weekly (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 36: IFN β-1b 250 µg every other day (Betaferon)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	267,900	-	6.924	-	-
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 37: Glatiramer acetate 20 mg SC once daily (Brabio), using list price

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	267,900	-	6.924	-	-
20 mg SC once daily (Brabio)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 38: Glatiramer acetate 20 mg SC once daily (Brabio), using interim price

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	267,900	-	6.924	-	-
20 mg SC once daily (Brabio)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 39: Glatiramer acetate 20 mg SC once daily/40 mg SC three times weekly (Copaxone)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	267,900	-	6.924	-	-
Glatiramer acetate 20 mg SC once daily (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years					

Table 40: IFN β-1b 250 µg every other day (Extavia)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	267,900	-	6.924	-	-
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 41: IFN β-1a 44/22 µg SC three times a week (Rebif)

Strategy	Mean cost (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	267,900	-	6.924	-	-
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					

5.6 Summary

In these analyses, we applied the discounted prices of disease modifying treatments made by each company, accounted for the costing structure identified by Teva and undertook pairwise analyses using pooled and individual treatment effectiveness estimates. As expected, having applied these reductions the results showed a decrease in the expected mean costs for the relevant drugs, and hence a reduction in the ICERs. In further exploratory analyses using a mortality multiplier also resulted in a reduction the ICERs.

Our preferred analyses (pooled analyses with AG mortality, committee preferred assumptions) in section 5.1 give:

- ICERs greater than £30,000 per QALY for [redacted]
- ICERs lower than £30,000 per QALY for [redacted]

6 References

1. Coyle P, Shang S, Castrillo-Viguera C. SC peginterferon beta-1a every 2 weeks demonstrated better clinical outcomes than SC interferon beta-1a TIW in patients with RMS, using a matching-adjusted comparison of 5 Phase 3 trials (P6.367). *Neurology* 2017;**88**.
2. Scott T, Shang S, Castrillo-Viguera C. A Matching-adjusted Indirect Comparison of Clinical Effectiveness of Subcutaneous Peginterferon Beta-1a and Intramuscular Interferon Beta-1a for the Treatment of Relapsing Multiple Sclerosis (P6.374). *Neurology* 2017;**88**.
3. Pokorski RJ. Long-term survival experience of patients with multiple sclerosis. *J Insur Med* 1997;**29**:101-6.
4. Jick SS, Li L, Falcone GJ, Vassilev ZP, Wallander M-A. Mortality of patients with multiple sclerosis: a cohort study in UK primary care. *Journal of Neurology* 2014;**261**:1508-17. http://dx.doi.org/10.1007/s00415-014-7370-3