**National Institute for Health and Care Excellence**

**MultipleTechnology Appraisal (MTA)**

**Beta interferon and glatiramer acetate for treating multiple sclerosis (review on TA 32)**

**Response to consultee and commentator comments on the draft remit and draft scope (pre-referral) – updated post invitation**

**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. This table was initially released in early January. However some consultation comments were excluded due to an administrative error. The comments table has therefore been updated to include all comments.

**Comment 1: the draft scope**

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| Background information | Association of British Neurologists | Estimates of the relative number of RRMS vs PPMS vary. 80% is the lowest end. There is a trend towards more patients being labelled with relapsing disease with time (Westerline H et al, P174 ECTRIMS, Barcelona, 2015). | Comment noted. The background section is intended to provide a brief introduction to the condition. No changes needed to the scope. |
| | Biogen | As noted in the scoping document, some products have different licences which in turn has implications for how precisely each product could be evaluated in accordance with its licence. | The technologies will be appraised within their marketing authorisations. No changes needed to the scope. |
| | Genzyme | Sentence four in paragraph 4 should read “For people with rapidly-evolving severe RRMS, natalizumab is recommended as a treatment option (NICE | The scope has been updated to state that |

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| | | Technology appraisal guidance 127). It is also noted that alemtuzumab's recommendation under TA312 also includes the rapidly-evolving severe RRMS population | alemtuzumab is used in people with active RRMS which reflects the NICE recommendation wording. |
| | Health Improvement Scotland | I think background information is appropriate | Comment noted. |
| | Merck Serono | Merck Serono generally agrees with the background information provided by NICE in the Scoping document. There are slight issues with terminology that could be addressed (such as "*periods of remission followed by relapses*" should be relapse followed by remission), but it does not distract from the definition of the decision problem. | Comment noted. |
| | MS society | (MS) is that the earlier treatment is administered the better the outcomes will be for the person diagnosed. This should be reflected in the background information as it is important that people with MS should be able to choose their first line of treatment when consulting with a neurologist. Please see the following links for more information:<br>MS Society website for further details<br>http://www.mssociety.org.uk/earlytreatment<br>The Association of British Neurologist's most recent guidelines<br>http://pn.bmj.com/content/early/2015/06/20/practneurol-2015-001139.full<br>The MS Brain Health initiative<br>http://www.msbrainhealth.org/<br>We would agree with points made by others that an additional statement should be included about non-pharmacological management of MS by a | The background section of the scope is intended to give a brief overview. It is anticipated that during the appraisal factors influencing outcomes, patient choice and non-pharmacological management will be discussed. |

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| | | multidisciplinary team of those with expertise in MS care. | |
| | MS Trust | There is growing clinical consensus about the importance of subclinical disease activity in relapsing remitting multiple sclerosis. This means that though relapses are important indicators of active disease and particularly for people living with MS, subclinical activity may challenge the concept of disease in remission.<br>We suggest amending the first paragraph to note that remission is defined not just by lack of clinical relapses but also lack of significant change in MRI. We note that the definition of 'significant change' needs clarification.<br>We also suggest adding in a statement about non-pharmacological management of MS by a multidisciplinary team of those with expertise in MS care. | Comments noted. The background section of the scope is intended to give a brief overview of the disease area and it is anticipated that what constitutes disease activity will be discussed during the appraisal.<br>The scope has focussed on the technologies being appraised. It is anticipated that non-pharmacological management within current practice will be discussed over the course of the appraisal. |
| | NHS England | The background information does not include the availability of the new copaxone formulation | The background section has been updated to state that a new formulation of copaxone is now available. |
| | Novartis | No comments | Comment noted. |

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| | Royal College of Nursing | Accurate – but need to be aware of the numbers of people with Multiple Sclerosis (MS) using these treatments and stating the benefits. | Comment noted. |
| | Teva UK Limited | Since Technology Appraisal 32 was published, in addition to interferon beta 1b (Extavia, Novartis) and a pegylated interferon beta 1a (Plegridy, Biogen Idec), glatiramer acetate 40mg/ml three times weekly (Copaxone, Teva Pharmaceuticals) has also been granted a marketing authorisation. Just like interferon beta 1b and pegylated interferon beta 1a, glatiramer acetate 40mg/ml was also not included in the Risk Sharing Scheme as it was not appraised in Technology Appraisal 32. Therefore in line with the rationale for the inclusion of the two beta interferons, it follows that glatiramer acetate 40mg/ml must also be included in this appraisal, so that guidance can be issued for both of the glatiramer acetate formulations currently licensed in the UK. | The background section of the scope has been updated to state that a new formulation of copaxone is now available. It is anticipated that the 40 mg/ml three times weekly formulation will be covered by this appraisal. |
| | UKMSSA | We suggest after the statement “There is currently no cure for MS.” and before going on to list the current pharmacological management there should be some reference to the holistic management of the condition by MS Specialists and through multidisciplinary interventions as found in the NICE Clinical Guideline for MS. (CG186). This would give a broader context to the MTA | Comments noted. The background section is intended to give a brief overview of the condition and treatment options. This appraisal is a review of TA32 and the background section has focused on technologies included in that appraisal and describing the risk sharing scheme and its implementation. |

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| The technology/ intervention | Association of British Neurologists | Yes | Comment noted. |
| | Biogen | The technologies to be appraised include pegylated interferon beta 1a (Plegridy) and interferon 1b (Extavia). Biogen would like guidance on the proposed modelling approach for these products given they are not part of the RSS and in turn are not included as part of the RSS cost-effectiveness model.<br><br>The draft scope does not mention the new glatiramer acetate (Copaxone) TIW formulation. Will this agent be included in the appraisal? | Comments noted. The Assessment Group will use the available data on technologies not included in the risk sharing scheme and apply these data in its model which will be based on the risk sharing scheme model. A description of the new formulation of glatiramer acetate has been added to the scope. |
| | Genzyme | We note that interferon beta 1a which is not pegylated may be administered subcutaneously (Rebif) or intramuscularly (Avonex). These drugs should be assessed separately however the wording used in the table on page 4 under the section “Interventions” would suggest that this will not be the case. | All interferon beta 1a, 1b and glatiramer acetate technologies with separate marketing authorisations will be appraised separately. |
| | Health Improvement Scotland | Yes, description of the technologies are accurate | Comment noted. |

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| | Merck Serono | Merck Serono considers each of the beta-Interferons as distinctive, in terms of their dosage, frequency/mode of administration and efficacy. This is reflected in their marketing authorisation. This should be made clearer in the scope, as there is a risk of presenting these products as identical to each other.<br><br>Specifically in the case of Rebif part of the label has been omitted from the scope "*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*." This was included with Betaferon, but is absent from Rebif's indication and could create misunderstandings later in the process if CIS is finalised within the scope. | Comments noted. All technologies with separate marketing authorisations will be appraised separately.<br><br>The scope has been updated to include the omitted text indicated by the company. |
| | MS Society | Yes | Comment noted. |
| | MS Trust | Copaxone (glatiramer acetate) should be included in both the daily and more recent (40mg) three times per week dosing schedule.<br><br>Rebif (interferon beta 1a) should include indications for clinically isolated syndrome (CIS) and also secondary progressive MS (SPMS) where relapses are still a feature. It should also mention both the 22mg and 44mg dosages. | The scope has been updated to note that a 40 mg formulation of glatiramer acetate is available and that this is not included in the risk sharing scheme.<br><br>The indication for Rebif has been updated. Different dosages are not normally listed in the scope. |
| | NHS England | Apart from the omission of the new copaxone formulation this is accurate | A description of the new |

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| | | | copaxone formulation has been added to the background section of the scope. |
| | Novartis | No comments | Comment noted. |
| | Royal College of Nursing | Yes, but new data needs to be reviewed and cannot be compared with the newer drugs as different criteria was used | Comment noted. The Assessment Group will carry out a systematic review of clinical and cost effectiveness data. |
| | Teva UK Limited | As per our comments in the 'Background Information', a description of glatiramer acetate 40mg/ml three times weekly is missing from this section, and should be added. The indication that is given for glatiramer acetate 20mg/ml once a day is correct. | Comment noted. A description of the new copaxone formulation has been added to the background section of the scope. |
| | UKMSSA | Yes | Comment noted. |
| Population | Association of British Neurologists | Regarding CIS, with this group convened and much of the literature appraised being relevant to both, it would seem reasonable to tackle the two concurrently. Treatment of CIS with indicators of risk is recommended by the 2015 ABN guidelines, but has not been considered by NICE. Practice varies across the country and the matter should be explored. The "two relapses in two years rule" restricting use of current drugs comes from the entry criteria to the original phase 3 trials. A high percentage of people in the CIS trials would now be classified as having MS (38% in REFLEX study - J Neurol. 2014 Mar;261(3):490-9) and the drugs appear to show a higher reduction in the relative risk of further relapse at this stage of the illness. Current prescribing | Comments noted. |

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| | | patterns are likely to see IFN/GA predominantly used early in the disease course, and considering the CIS/early MS papers along with the established RRMS papers might reflect current and future use more accurately.<br>Not all people with CIS will develop MS, but increasingly complex predictor models exist to identify high risk patients within defined time scales**.** | |
| | Biogen | Biogen believes the population should be those people with relapsing remitting multiple sclerosis (RRMS) that is not highly active.<br><br>Not all agents are licensed for a single demyelinating event or secondary progressive multiple sclerosis and it is therefore unclear as to how the differing licences will be handled in the MTA for the individual products. Biogen would also like to draw NICE's attention to the lack of direct comparability resulting from the heterogeneity between the reference products. For example, it would not be expected that a patient with RRMS would necessarily respond in the same way to a treatment as a secondary progressive multiple sclerosis (SPMS) patient, not least due to clinical differences. | The population has been updated to:<br>People with relapsing remitting multiple sclerosis (including people with relapsing remitting multiple sclerosis and people with secondary progressive multiple sclerosis with active disease, evidenced by relapses)<br>People with clinically isolated syndrome, that is, a single demyelinating event, who are considered at high risk of developing multiple sclerosis<br>This is a broad description to cover all indications across the |

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| | | | range of technologies being appraised. Technologies will be appraised according to their marketing authorisation. |
| | Genzyme | We would suggest that the appraisal for clinically isolated syndrome (CIS) should be carried out separately to that for active RRMS. This is supported by the fact that the clinical effectiveness dataset and the parameters in the health economic model for CIS will be different to those for RRMS (eg. drug efficacy and natural history progressionestimates). In addition it is noted that the Risk Sharing Scheme did not collect information on CIS. | Comments noted. The population has been updated to list CIS separately. |
| | Health Improvement Scotland | It is OK.<br>Although interferons have been used as off-label medication in paediatric population, I wonder if a specific comment for MS people age 16-18 would be adequate. | Comment noted. NICE can only issue recommendations within a technology's marketing authorisation. |
| | Merck Serono | Merck Serono agrees with the population outlined in the scope. | Comment noted. The population has been updated to list MS and CIS separately. |
| | MS Society | Population should be multiple sclerosis where relapses are a major feature.<br>People with Clinically Isolated Syndrome should not be considered within the population for this MTA and should be appraised under a separate STA. The treatment effect in CIS and MS should be considered in separate appraisals due to the differing levels of evidence. See the answers to 'questions for | Comment noted. The scope has been updated to list MS and CIS separately. Furthermore the |

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| | | consultation' for more information. | definition of the MS population now is:<br>People with relapsing remitting multiple sclerosis (including people with relapsing remitting multiple sclerosis and people with secondary progressive multiple sclerosis with active disease, evidenced by relapses). |
| | MS Trust | Population should be multiple sclerosis where relapses are a major feature. | The population has been updated to state 'people with relapsing remitting multiple sclerosis (including people with relapsing remitting multiple sclerosis and people with secondary progressive multiple scleroisis with active disease, evidenced by relapses) in order to cover all populations covered by the marketing authorisations. The |

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| | | | population with clinically isolated syndrome has been listed separately. |
| | NHS England | Yes | Comment noted. |
| | Novartis | No comments | Comment noted. |
| | Royal College of Nursing | No comments | Comment noted. |
| | Teva UK Limited | The population 'people with multiple sclerosis' would include secondary and primary progressive multiple sclerosis, and certainly none of the technologies are licensed for the latter, with only interferon beta 1b being licensed in the former. People with 'relapsing forms of multiple sclerosis' would be the appropriate population, as it encompasses the indications of the technologies being assessed. | Comment noted the scope has been updated to define the MS population:<br>People with relapsing remitting multiple sclerosis (including people with relapsing remitting multiple sclerosis and people with secondary progressive multiple sclerosis with active disease, evidenced by relapses).<br>Recommendations will be made within each technology's marketing authorisation. |

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| | UKMSSA | It may be more appropriate to identify the population as being Relapsing Remitting MS (RRMS) or Secondary Progressive MS where relapses are still a feature. Clinically Isolated Syndrome was not identified in the original TA32 and may need to be considered separately due to data collection issues. | Comment noted. The MS and CIS populations this appraisal will cover are now listed and defined separately. |
| Comparators | Association of British Neurologists | Even though we recognise that in 2015 a patient with 2 relapses in 2 years would rarely be considered for conservative observation/best supportive care alone, I agree with the choice of best supportive care, building on the work of the risk sharing scheme. The cost of comparator therapies are themselves currently linked to the RSS cost of IFN/GA, making such a design meaningless. | Comments noted. |
| | Biogen | Comparisons to best supportive care (BSC) and active treatment (each interventions compared to each other) are listed as the comparators in the scope. Clarification is needed on the primary comparator for the MTA analysis, particularly given the inclusion of Plegridy and Extavia in the scoping document. | Comments noted. The scope states that best supportive care is the comparator and if appropriate (meaning if evidence allows and if the populations covered by the marketing authorisations permit) the technologies will be compared with each other. The NICE reference case states that a fully incremental analysis is preferred. |
| | Health | OK. | Comments noted. The |

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| | Improvement Scotland | Obs: First clinical trials evaluated efficacy and safety of interferons against placebo in MS. At the moment, the "best alternative care" can not include any placebo therapy, as most of active MS patients are modifying disease therapies. | 'other considerations' section of the scope states: 'It is recognised that best supportive care without a disease modifying treatment is not current established clinical practice for treating relapsing remitting multiple sclerosis. Best supportive care was the comparator for beta interferon and glatiramer acetate in TA32 and therefore is included as the comparator for this appraisal.' |
| | Merck Serono | Merck Serono agrees with the recognition within the scoping document that BSC is no longer an option for MS patients in the UK. However, as the Risk Share Scheme model and results are to be used as the basis for the appraisal, we understand for the need in this instance for BSC (as represented by the British Columbia natural history model), to feature uniquely in this particular analysis.<br>Similarly, in this case we would emphasise that it would be inappropriate for the beta interferons and glatiramer acetate to be compared with each other using the RSS results. As outlined in the original Health Service circular:<br>"*The scheme relates solely to the cost effectiveness of the use of these products in the NHS; it is not intended and should not be represented as a* | Comments noted. |

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| | | *further "clinical" trial of the clinical efficacy of the products concerned which have, of course, already been licensed on the basis of their safety, quality and efficacy."*[1]<br>These products have all entered the scheme with different target hazard ratios (HR's) and were intended to be assessed independently against natural history, not against each other. Using the data comparatively across the products would be against the original design of the scheme and would be subject to bias. Any comparisons between products, should be based on evidence synthesis of the relevant clinical trials. Before any comparisons are made between products, we would ask for clarity on the methods to be applied.<br><br>**http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4012214.pdf igitalasset/dh_4012214.pdf** | |
| | MS society | Comments on best supportive care are made below in the 'other considerations' section.<br><br>We agree that, where appropriate, the drugs should be compared to each other | Comments noted. |
| | MS Trust | Comments on best supportive care are made below in the 'other considerations' section.<br><br>We agree that, where appropriate, the drugs should be compared to each other. | Comments noted. |
| | NHS England | Suggest addition of teriflunomide and dimethyl fumarate as appropriate | Comments noted. The |

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| | | comparators as we would consider these to be disease modifying treatments and would therefore be excluded under the current description | aim of this appraisal is to determine whether the interferons and glatiramer acetate, which were not recommended in TA32 (and new interferon and glatiramer acetate technologies) are now cost effective. For this reason NICE have included best supportive care, which was the comparator in TA32 and has been used as a comparator in the risk sharing scheme. |
| | Novartis | Since “best supportive care” is included as a comparator within the draft scope, it would be helpful if a definition of the interventions included within this term could be included in the scope. | Comment noted. We do not define best supportive care in the scope. The Appraisal Committee will discuss what constitutes best supportive care. |
| | Royal College of Nursing | These treatment (except plegridy) have been used for nearly twenty years in the NHS. Any decision on their future use must take into account those people that currently use these drugs very effectively. | Comment noted. |

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| | UKMSSA | The Risk Sharing Scheme developed a model that used an untreated natural history cohort from British Columbia Canada as a comparator. We believe this provides robust comparative evidence. | Comment noted. |
| Outcomes | Association of British Neurologists | I would avoid the term freedom from disease activity. No evidence of clinical disease activity (relapse or disability worsening) should be used. MR will often show considerable subclinical activity in this group, even when apparently stable. | Comment noted. The outcome freedom from disease activity has not been defined further in the scope because it is anticipated that freedom from disease activity may be defined differently in different clinical trials. It is anticipated that the most appropriate definition of this outcome for the purposes of appraising cost effectiveness will be determined during the appraisal. |
| | Biogen | Further guidance is needed on the listed outcomes.<br><br>With regard to freedom from disease activity as an outcome of interest, this can be measured in a number of different ways. Typically freedom from disease activity is referred to as No Evidence of Disease Activity (NEDA), and multiple versions of NEDA exist. Biogen therefore request further clarification on the precise definition of freedom from disease activity, or NEDA, if the intention is to include this composite measure. Furthermore, this outcome | Comments noted.<br><br>The outcome freedom from disease activity has not been defined further in the scope because it is anticipated that freedom from disease activity may be |

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| | | measure is one that would not have been captured in all trials and guidance is needed on how this will be handled in the appraisal.<br>It will be important that key outcomes such as EDSS and severity of relapse and adverse events (AEs) are captured appropriately within the economic approach especially given previous challenges from the original RSS model and NICE appraisal in 2002 (Beta interferon and glatiramer acetate for the treatment of multiple sclerosis [TA32]).<br>In terms of health-related quality of life, it will be important to capture caregiver disutility resulting from MS. This is consistent with the NICE Reference Case, which makes provision for including such data as part of QALY calculations. | defined differently in different clinical trials. It is anticipated that the most appropriate definition of this outcome for the purposes of appraising cost effectiveness will be determined during the appraisal.<br>Caregiver utility may be considered within the cost utility analysis. |
| | Health Improvement Scotland | Yes. I think most important outcomes include relapsing rate, severity of relapses, disability progression, fatigue, cognition, and freedom from disease activity. However I feel that there have not been adequate clinical trials to assess the impact of these modifying disease therapies on cognitive function in MS.<br>Tolerability and adverse effects is also an important outcome to be evaluated.<br>We have only few scales to assess disability in MS. The EDSS has been criticised regarding its psychometric properties; in the futures new scales are needed to assess the full range of disability on MS. | Comments noted |
| | Merck Serono | Merck Serono agrees that all the outcomes determined in the scope should be included in the clinical and cost-effective discussions. We would like to suggest that MRI activity is also included in the reporting. This may not have an impact on the modelling component of dossier, but may be of clinical benefit to Health Care Professionals (HCP's). | Comment noted. MRI activity has not been listed as an outcome because the scope aims to identify measures of health |

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| | | | benefit that are important to patients and/or their carers. However, the most appropriate definition of the outcome freedom from disease activity will be determined over the course of the appraisal. It is anticipated that this will consider whether freedom from disease activity means no clinical symptoms, MRI activity or both. |
| | MS Society | In considering freedom from disease activity, which is welcome, value should also be given to steps towards that goal in terms of suppression of disease activity.<br><br>To gain a fuller understanding of disease activity a full range of indicators should be acknowledged both clinical and subclinical. Understanding of disease activity in MS is evolving with greater emphasis being placed on symptoms beyond relapse rates and disability progression such as the number of lesions on MRI scans and brain atrophy.<br><br>Further indicators should also be included. In 2015, a panel of MS experts proposed the inclusion of measures of cognition, fatigue and depression in the definition of disease activity, as these patient-reported outcomes contribute substantially towards quality of life in people with MS. (Brain Health Report) | Comments noted.<br><br>The outcome freedom from disease activity has not been defined further in the scope because it is anticipated that freedom from disease activity may be defined differently in different clinical trials and may include MRI activity, clinical symptoms or both. It is anticipated that the most appropriate |

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| | | | definition of this outcome for the purposes of appraising cost effectiveness will be determined during the appraisal.<br>The scope includes symptoms such as fatigue, cognition and visual disturbance. |
| | MS Trust | Yes, we agree that these outcome measures capture the most important health benefits, though we highlight the following issues which we believe will need further clarification early in the technology appraisal process:<br>Symptoms - instrument selection for outcome measurement for symptoms such as fatigue and cognition in MS is still an evolving area. Multiple instruments are currently in use across clinical trials in MS and it will be important to critically consider instrument selection as well as the results they demonstrate in the data submitted. There is also no clear measure for assessing the severity of relapses.<br>Freedom from disease activity is also an evolving concept in MS and there is not yet a fully settled definition of the term, particularly with respect to the critical measures of sub-clinical disease activity. Some definitions include measurement of total brain volume or other measures of brain atrophy in addition to presence of brain lesions on MRI scans. To be useful in the clinical setting, the exact detail of the outcome measure needs further clarification and definition to guide prescribing and to help people living with MS understand the goals of treatment and help them in making their treatment choices. This may be best facilitated by separating out the measures aggregated in the concept of freedom from disease activity. For | Comments noted.<br>The outcome freedom from disease activity has not been defined further in the scope because it is anticipated that freedom from disease activity may be defined differently in different clinical trials and may include MRI activity, clinical symptoms or both. It is anticipated that the most appropriate definition of this outcome for the purposes of appraising cost effectiveness will |

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| | | instance, number of lesions on MRI scans, as the prime sub-clinical measure may be best treated as a separate measure. The MS Trust supports greater attention to clinical and sub-clinical measures of disease activity in RRMS to inform treatment strategies and a more proactive approach to initiating treament with a DMD early and an escalation strategy if evidence of disease activity is present on current treatment. | be determined during the appraisal.<br>Similarly other outcomes have been kept broad and have not been explicitly defined to allow flexibility in the appraisal and to allow these to be defined on the basis of available evidence. |
| | NHS England | Yes | Comment noted |
| | Novartis | No comments | Comment noted |
| | Royal College of Nursing | Again as above, these drugs are relatively cost effective for those people with MS that they work for, we need to keep choice within the disease modifying treatments (DMTs) realm. These are safe and well researched | Comment noted |
| | Teva UK Limited | In general they do, though would be important to include neutralizing antibodies in this list on account of their impact on efficacy. | Comment noted. Presence of neutralising antibodies has been added as an outcome |
| | UKMSSA | These outcome measures capture the most important benefits but may need further clarification. For example:<br>Severity of relapse is identified as an outcome but there is currently no universal objective scale used as a means of measuring this outcome. | Comments noted. It is anticipated that the exact definition of the outcomes will be discussed during the |

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| | | Similarly “freedom from disease activity” needs clarification in order to establish if this relates to symptomatic presentation or sub clinical radiological measures such as lesion accumulation as identified by MRI scanning. (The European Medicines Agency has recognised that MS may be defined as active on radiological *or* clinical eveidence.) | appraisal. |
| Economic analysis | Association of British Neurologists | As Betaferon and Extavia are identical and share a literature dataset, a comment on one (allowing for correction of any price differential) will allow conclusions on the other to be easily drawn. Plegridy should be considered as a potential advance in promoting compliance, but with limited data at the time of approval.<br>While acknowledging the choice of a model based on utility to determine cost-effectiveness, this will potentially underestimate the impact of early loss of employment and the indirect costs and burden on informal carers. | Comments noted. All technologies will be appraised separately. The appraisal process allows consideration of factors not included in the QALY calculation. Caregiver utility may be considered within the cost utility analysis. |
| | Biogen | The draft scope states that the economic model will be based on the model used in the RSS and updated with new data from the RSS. Can NICE confirm if this will be with data from year 10 and will formal SAG sign off be required before use?<br><br>Further discussion is needed on how company contributions and investment in the infrastructure of MS services will be handled within the assessment. It should be noted that these constitute a significant part of the overall RSS arrangement.<br><br>Is there a standardised way manufacturers should consider and capture the socioeconomic costs of MS to be used for modelling purposes as part of additional scenario analysis to capture the wider burden of the disease? This | Comments noted. The Department of Health has indicated that 10 year data from the risk sharing scheme (RSS) with its scientific advisory group sign off will be made available to NICE for the purpose of this appraisal.<br><br>It is anticipated that the way the RSS has contributed to current infrastructure for MS will |

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| | | is particularly relevant given there is evidence to suggest that a significant proportion of the MS disease burden falls in social and community care.<br><br>Treatment waning is recognised as a potential clinical and epidemiological phenomenon associated with treatments for MS whereby attrition of benefit is observed over time. Biogen would welcome guidance as to how this should be considered in the modelling approach and associated statistical methods.<br><br>The ICER within the RSS was agreed at £36,000 per QALY. To ensure analytical consistency between the RSS and the MTA, Biogen believes that the threshold should remain at £36,000 per QALY; a point also discussed at the previous pre-scoping meeting for this MTA.<br><br>As has since been acknowledged following NICE TA 32 in 2002 (Beta interferon and glatiramer acetate for the treatment of multiple sclerosis), the current RSS model does not handle relapses and their associated impact adequately. As noted in the scoping document, relapse rates and severity of relapses are included as important outcomes. Biogen therefore requests further guidance on how NICE intends to adequately capture relapses, and their impact, in the MTA assessment.<br><br>There is no reference as to how natural history data will be addressed in the MTA model. Currently, the RSS model uses the British Columbia database. However, it should be noted that there is a mix of RRMS and SPMS patients in this target population. Biogen requests further clarification on how the potential impact of SPMS patients on the transition probabilities within the analysis will be considered as part of the outcomes in the RSS model. | be discussed in the appraisal.<br><br>The NICE reference case stipulates that costs included in the modelling should be from an NHS and personal social services perspective. Benefits of treatment not captured in the QALY calculation may also be discussed during the appraisal.<br><br>NICE does not have a single threshold for establishing whether a technology is cost effective. The recommendations take into account the estimated incremental cost-effectiveness ratio (ICER), the degree of uncertainty surrounding this estimate and other factors such as benefits that are not captured by the economic model (see section 6.3.3 of the NICE methods to the |

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| | | | guide of technology appraisal).<br>It is anticipated that any clinically relevant subgroups will be identified during the appraisal. |
| | Genzyme | We note the following statement has been included within this section:<br>"If appropriate, any continuing contributions made by the companies who manufacturer technologies for multiple sclerosis to the infrastructure for multiple sclerosis management, should be taken into account in determining cost effectiveness."<br>We would question whether the inclusion in a cost effectiveness analysis of such continuing contributions to infrastructure costs made by manufacturers is consistent with NICE technology appraisal methodology: | Comments noted. It is anticipated that during the appraisal the contribution of companies to the infrastructure management over the period the RSS has been in operation and future contributions once the risk sharing scheme has ended will be discussed. |
| | Health Improvement Scotland | Time horizon is appropriate | Comment noted. |
| | Merck Serono | Merck Serono is aligned with NICE's proposal to utilise the RSS results and cost-effectiveness model for the purpose of this appraisal. We suggest that the model is used as the basis for the assessment, but with considerations towards the reference case.<br>We suggest the time horizon should be in line with previous submission (50 | Comments noted. |

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| | | years). In terms of a waning effect, we propose that any consideration of this topic should reflect the RSS data. If the products have met their targets consistently up to the final analysis at 10 years, then any waning effect of these products should only be assumed after this point. | |
| | MS Society | There is a concern over how the data derived from the risk sharing scheme will be used to analyse plegridy and extavia, two interferons which were not part of the original TA 32 or the resulting risk sharing scheme. Clarification is needed on how these two additions will be given equivalent value to the older products and analysed using risk sharing scheme data.<br><br>The section on economic analysis includes this following statement:<br>*'If appropriate, any continuing contributions made by the companies who manufacturer technologies for multiple sclerosis to the infrastructure for multiple sclerosis management, should be taken into account in determining cost effectiveness'*<br>This statement requires more specification if it is to be fairly implemented. The contributions should be restricted only to those made under the terms of the RSS and should be standardised. If this cannot be achieved, it will be difficult to equitably apply these costs. Any additional ad hoc investments in infrastructure made by the four manufacturers during the term of the RSS should be excluded.<br><br>The statement, "costs will be considered from an NHS and Personal Social Services perspective" does not adequately address the costs to patients and carers or to society and the economy in general. MS can have a devastating effect on a person's ability to remain in employment and on the levels of informal care they require. A report by the Work Foundation found that 80 per cent of PwMS stop working within 15 years of the onset of diagnosis and 44 per cent retire early because of the condition (Bevan, S., Zheltoukhova, K., | Comments noted. It is anticipated that data for extavia and plegridy will be obtained from literature searches and the company submissions.<br>Comment on infrastructure contributions noted.<br><br>The NICE reference case stipulates what can and can't be included in the cost–utility analysis. The appraisals process welcomes comments from patient groups on how the condition and |

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| | | McGee, R. and Blazey L. (2011) Ready to Work? Meeting the Employment and Career Aspirations of People with Multiple Sclerosis. London: Work Foundation). The MS Society found 82 per cent of respondents in a 2010 survey had at some point during a relapse been unable to carry out their paid employment (MS Society, 2010).<br><br>Consequently the appraisal committee should take into account:<br>- Ability to remain in the workforce and reduce adsenteeism (Increasing the ability of people with MS to remain in work reduces social security costs relating to unemployment and sickness benefits. Currently 21,400 people with MS are claiming Employment and Support Allowance (Department of Work and Pensions))<br>- Independence for carers (The Work Foundation report found that the "professional careers of 57 per cent of relatives are adversely affected by MS of a family member 2011: 4)<br>- The value of informal care http://circle.leeds.ac.uk/files/2012/08/110512-circle-carers-uk-valuing-carers.pdf<br>- The impact of informal care on carers - 87 per cent said caring for a family member or friend has had a negative impact on their mental health and 64 per cent of carers blamed their poor health on a lack of practical support and 50 per cent on not enough financial support (In Sickness and in Health, 2012, Carers Week).<br>- Reduction in disability benefits such as Disability Living Allowance, Personal Independence Payment and Carer's Allowance, due to reduced burden of disease. Over 60,000 people with MS claim either DLA or PIP. Under DLA 94% claimants with MS received the higher rate mobility component and 41% higher rate of the car component. (Department of Work and Pensions)<br>- Increased tax revenue (Kennedy, 2009: 27)<br>It must be taken into account that MS is frequently both a fluctuating and | treatment affects their lives and this is taken into account by the Appraisal Committee. |

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| | | chronic progressive condition that has a significant impact on the quality of life of individuals with the condition and also the lives of family members. | |
| | MS Trust | The section on economic analysis includes this following statement:<br><br>*If appropriate, any continuing contributions made by the companies who manufacturer technologies for multiple sclerosis to the infrastructure for multiple sclerosis management, should be taken into account in determining cost effectiveness.*<br><br>When preparing our response to the draft scope we requested clarification on this statement, however we have had no response from NICE.<br><br>This statement requires more specification if it is to be fairly implemented. The contributions should be restricted only to those made under the terms of the RSS and should be standardised. If this cannot be achieved, it will be difficult to equitably apply these costs. Any additional ad hoc investments in infrastructure made by the four manufacturers during the term of the RSS should be excluded.<br><br>The draft scope states that costs will be considered from an NHS and Personal Social Services perspective.With more examples of integrated health and social care budgets, economic cases based on a distinction between the two cost domains are less relevant for commissioners and payers. There is greater scope for recognising that costs avoided in social care should be included in analysis of a healthcare intervention.<br><br>For MS, the impact of reducing the frequency and severity of relapses can have on work presenteeism is also significant, delivering individual and societal benefit that are not taken into account in current economic analyses by NICE. | Comment noted on infrastructure. NICE included this statement in the scope to reflect the fact that, as part of the RSS, some companies contributed to the infrastructure of multiple sclerosis care. During the appraisal, companies have the opportunity (if relevant) to present ways they intend to contribute to infrastructure in the future.<br><br>The NICE reference case includes both NHS costs and personal social services costs. Any savings in personal social services associated with treatment can be included in the modelling, if supported by evidence.<br><br>The NICE reference |

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| | | | case does not include wider societal costs, such as changes in productivity. Nonetheless, NICE welcomes comments from patient experts about how MS and the technologies impact on their lives. |
| | NHS England | None | Comment noted |
| | Novartis | *"The economic model will be based on the model used in the risk sharing scheme, including any changes that have been made to the model since 2002. The model parameters and inputs will be updated where necessary to reflect current costs, the NICE reference case and current practice, and any new data from the risk sharing scheme"*<br>The above statement appears to imply that only one model will be used for this MTA review. Can NICE confirm whether this is the case and whether Novartis is free to submit a model of its own, as would usually be the case in an MTA?<br>Novartis would also like to receive details (and/or meeting minutes) of any agreement on the model specification and input parameters as we have not been involved in these discussions. We also request that any new data from the risk share scheme used to inform model parameters, should be shared with Novartis at the same time as with other consultees<br>*If appropriate, any continuing contributions made by the companies who manufacturer technologies for multiple sclerosis to the infrastructure for multiple sclerosis management, should be taken into account in determining* | Comments noted. It is anticipated that the assessment group will use the RSS model as a basis for its model. Companies are welcome to submit their own models as part of the multiple technology appraisal process.<br>The Department of Health has agreed to share 10 year data from the RSS with sign off from its scientific advisory group. The Assessment Group will determine how the data |

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| | | *cost effectiveness.*<br>Regarding the above statement, Novartis would like to receive further details of the process by which infrastructure contributions will be taken into account in cost effectiveness calculations and how this process has been determined.<br>Novartis would also be grateful for clarification from NICE as to how the above statement aligns with the guidance on evaluating cost-effectiveness described in the 2013 NICE Methods Guide. | is used for its modelling. Please note that the methodology used in the RSS model and results from shorter follow up periods have been published.<br>The Assessment Group will use the RSS model as a basis for developing a model that meets the NICE reference case. The Assessment Group's model will be made available to all companies at the same time. |
| | Royal College of Nursing | Again these are relatively cheap compared to the newer DMTs, they offer a viable alternative for people and are well tolerated by many with minimal side effects | Comment noted |
| | UKMSSA | Costs identified ( "NHS and Personal Social Services Perspective) should also include those relating to time lost at work and or loss of employment- a significant personal and societal cost in working age adults with RRMS. | Costs relating to time lost at work or loss of employment are not included in the cost–utility calculations. However, NICE |

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| | | | welcome comments from patient groups about how the condition and treatment impacts their lives and this is considered by the Appraisal Committee |
| Equality and Diversity | Biogen | No comment | Comment noted |
| | Health Improvement Scotland | Several factors should be taken into account: 1) geographical dispersion of the community and difficulty to access rapid and specialized medical assessment; 2) limitations to access MS nurses, neurology consultants and neuropsychologists; 3) difficulties to access standard rehabilitation care; 4) functioning of “drug home delivery” companies; 5) quality of the different injection devices used either with interferons or copaxone | Comments noted. The Committee will discuss whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population. |
| | Merck Serono | Merck Serono envisages no equality issues in relation to this appraisal. | Comments noted. |
| | MS Trust | None | Comment noted. |
| | NHS England | None | Comment noted. |
| | Novartis | No comments | Comment noted. |
| | Royal College of Nursing | No comment | Comment noted. |

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| | UKMSSA | None | Comment noted. |
| Other considerations | Association of British Neurologists | While this exercise has been anticipated since the initial 2002 assessment, it is noteworthy that long term models assuming persistence with one of these drugs are intrinsically flawed. Failure on these drugs will drive an increasingly early treatment switch and any issues with tolerability are likely to lead to a switch to an oral. A real world observational study, already out of date, (Jokubaitis PLoS One. 2013;8(3):e59694) has shown median time to switch off a first drug is 2.5 years, challenging the rationale of modelling the long term cost effectiveness of monotherapy, rather than considering treatment strategies. The arrival of the more potent biological agents and potentially more acceptable oral drugs is making it difficult to identify the cohort of patients that will be started IFN/GA and, particularly, identifying the group of patients who are likely to remain on them long term. One could assume that only high responders will be left on IFN/GA past the first few years. | Comments noted. |
| | Bayer | **Do you consider beta interferon and glatiramer acetate to be innovative in their potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?**<br>The beta interferons, as a class, continue to offer people with relapsing multiple sclerosis (MS) advantages over no treatment. For interferon beta-1b (Betaferon) these effects have been demonstrated in large, randomised controlled studies in terms of significantly reduced relapse frequency and severity, lower number of MS-related hospitalisations(1), a highly significant and sustained reduction in disease activity on magnetic resonance imaging evident soon after treatment onset (2), and evidence of slowing of disability progression (3,5). In a large, placebo-controlled study, patients with clinically isolated syndrome (CIS) at high risk of clinically definite MS who received early treatment with interferon beta-1b demonstrated a decrease of almost half in conversion to clinically definite MS over 2 years compared to placebo | Comments and references noted. |

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| | | (p < 0.0001) (4). Early treatment in this study was also associated with a reduced risk for progression of disability of 40% compared with delayed treatment over 3 years (5). The impact on early relapse rate on long term disease progression in MS has previously been well-established (6). There are also data to suggest that beta-interferons as a class may slow progression of cognitive impairment (5,7). Interferon beta-1b was the first licensed treatment for MS and safety data have now been published from up to 21 years of follow-up of patients enrolled in the original phase III clinical trials (8, 9). No unexpected adverse events were identified in long term use, and there was an observation that early treatment with interferon beta-1b for up to 5 years was associated with a 46.8% lower risk of death compared to patients originally randomised to placebo, irrespective of intervening treatment (9). Highly innovative at the time they were introduced, the beta interferons remain a valuable alternative to the more recently licensed disease-modifying therapies, particularly in younger people with relapsing MS and those with early and/or less aggressive disease, because of their efficacy in controlling relapse rate and severity, coupled to a very well-established, predictable and tolerable safety profile demonstrated in large populations over more than two decades.<br><br>**References**<br><br>1. IFNB Multiple Sclerosis Study Group. Interferon β-1b is effective in relapsing-remitting multiple sclerosis. I: clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 1993; 43: 655– 661<br>2. IFNB Multiple Sclerosis Study Group. Interferon β-1b is effective in relapsing-remitting multiple sclerosis. II: MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. | |

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| | | Neurology 1993; 43: 662– 667.<br>3. European Study Group on Interferon 1-1b in Secondary Progressive MS. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. Lancet. 1998; 352: 1491–1497<br>4. Kappos L. et al Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes Neurology 2006;67:1242–1249<br>5. Kappos L et al Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study. Lancet 2007; 370: 389–97<br>6. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. I: clinical course and disability. Brain 1989; 112: 133– 146<br>7. Mokhber N et al. Cognitive dysfunction in patients with multiple sclerosis treated with different types of interferon beta: A randomized clinical trial.J Neurol Sci. 2014 Feb 4. pii: S0022-510X(14)00062-8. doi: 10.1016/j.jns.2014.01.038. [Epub ahead of print]<br>8. Kappos L, Traboulsee A, Constantinescu C, et al. Long-term subcutaneous interferon β-1a therapy in patients with relapsing-remitting MS. Neurology 2006; 67: 944– 953.<br>9. Goodin D.S. et al Survival in MS: A randomized cohort study 21 years after the start of the pivotal IFNβ-1b trial Neurology 2012 vol. 78 no. 17 1315-1322<br><br>**Do you consider that the use of beta interferon or glatiramer acetate can** | Comments noted. |

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| | | **results in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?**<br>The integrity of normal physiological functioning in a diverse number of areas including neurological function, neuropsychiatric function like cognitive impairment, mood disorder and psychosis, and other areas such as mobility and fatigue can affect the Health Related Quality of Life (HRQoL) of people affected by MS([1]). In order to capture the impact of RRMS and SPMS on patient's HRQoL, a large variety of MS-specific QoL measures have been developed over the years. However, generic instruments such as EQ-5D are widely used and accepted for the assessment of patient's quality of life in clinical studies. These generic HRQoL measures were developed without a specific disease in mind and are therefore applicable to a wide range of populations. Their main disadvantage is that they are not accurate enough to capture topics of particular relevance to people affected by MS such as cognitive complaints for example. As a consequence of their relatively poor coverage of the MS-specific symptoms, these instruments result less responsive to treatment-induced changes than the MS-specific measures([Error! Bookmark not defined.]). In support of this there is a study by Hemmett et al (2004) which showed that a group of people treated with beta interferon reported a significant higher mean EQ-5D score compared to people not treated with beta interferon. However, despite the better EQ-5D score, the impact of fatigue and lack of vitality on the HRQoL of those patients did not receive sufficient recognition as not directly captured in the EQ-5D measure([2]).<br><br>[1] Benito-Leon J, Morales JM, Rivera-Navarro J et al. A review about the impact of multiple sclerosis on health-related quality of life. Disabil Rehabil 2003; 25:1291-1303<br>[2] Hemmett L, Holmes J, Barnes M, et al. What drives quality of life in multiple sclerosis? QJM 2004; 97:671-676 | |

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| | Health Improvement Scotland | Compliance and adherence to treatment are other important issues to be taken into account | Comment noted |
| | Merck Serono | As outlined in the HSC' the original targets set for the scheme were based on a cost-effectiveness threshold of £36,000. This was established after deliberations with NICE and the consideration of other factors that could not be captured within the RSS model:<br>I. the impact of treatment on the severity (independent of the frequency) of relapses, and<br>II. Possible cost offsets from the avoidance of severe levels of disability requiring intervention by the Personal Social Services1.<br>We would like these factors to be also considered when the RSS model is used for this assessment. | Comment noted. The Appraisal Committee will discuss any benefits of treatment that are not included in the economic model. |
| | MS society | **Comparators**<br>We agree that best supportive care does not represent established clinical practice in the management of RRMS. No recent technology appraisals in RRMS have used best supportive care as the comparator and the MS Society, along with others, have consistently argued against its use. We do, however, recognise that the RSS is an exceptional case and at the time that the original TA32 was undertaken, in the absence of any other licensed disease modifying treatments, best supportive care was indeed the only comparator.<br>Whilst in no way accepting best supportive care as a legitimate comparator in other circumstances, we agree that it is appropriate to be used in the context of this MTA on the basis that the only analysis being undertaken is on data from the observational study comparing the four agents to natural history data over 10 years using the analytical model developed during the scheme and which was used for the latest mid-term data analysis. This would answer the | Comments noted |

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| | | question originally posed when the RSS was first established. We believe that this choice is right for people with RRMS, those currently on treatment and those who may be making treatment choices in the future.<br>We recognise that the analysis will not answer the other and perhaps more current issue regarding the use of these agents by the NHS in the context of other recommended treatments and current clinical practice. We accept this limitation and agree that is necessary in order to complete TA32. | |
| | MS Trust | We agree that best supportive care does not represent established clinical practice in the management of RRMS. No recent technology appraisals in RRMS have used best supportive care as the comparator and the MS Trust, along with others, have consistently argued against its use. We do, however, recognise that the RSS is an exceptional case and at the time that the original TA32 was undertaken, in the absence of any other licensed disease modifying treatments, best supportive care was indeed the only comparator.<br>Whilst in no way accepting best supportive care as a legitimate comparator in other circumstances, we agree that it is appropriate to be used in the context of this MTA on the basis that the only analysis being undertaken is on data from the observational study comparing the four agents to natural history data over 10 years using the analytical model developed during the scheme and which was used for the latest mid-term data analysis. This would answer the question originally posed when the RSS was first established. We believe that this choice is right for people with RRMS, those currently on treatment and those who may be making treatment choices in the future.<br>We recognise that the analysis will not answer the other and perhaps more current issue regarding the use of these agents by the NHS in the context of other recommended treatments and current clinical practice. We accept this limitation and agree that is necessary in order to complete TA32. | Comments noted. |
| | NHS England | None | Comment noted. |

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| | Novartis | No comments | Comment noted. |
| | Royal College of Nursing | Please see above | Comment noted. |
| Questions for consultation | Health Improvement Scotland | Pregnancy issues related with modifying disease therapies in MS should also be taken into account. | Comment noted. |
| | Merck Serono | In the case of including Clinically Isolated Syndrome (CIS) within the appraisal, Merck Serono is broadly supportive. We feel that patients diagnosed and treated at the earliest possible period of their disease, have the greatest opportunity of slowing its progression. Patterns of treatment across the UK are still patchy and while is some areas, CIS is not a concern, (due to patients receiving confirming diagnosis with an MRI scan), there are situations where the diagnosis and treatment of CIS could improve the overall treatment rates and outcomes of patients with this progressive disease.<br>Merck Serono cannot deliberate on other technologies, but Rebif has clinical evidence of its efficacy in CIS[2] and its marketing authorisation also includes this indication.<br>However, Merck Serono would hesitate including CIS within the scope if it could not be assessed under the present proposal. We feel that any decision on CIS could be made on clinical merits and do not require expansion of the economic components of the scope.<br>In relation to expanding TA32, Merck Serono strongly disagrees with the inclusion of Plegridy and Extavia within this appraisal.<br>This review is primarily based on the results from the RSS and utilising the RSS model. Neither Plegridy nor Extavia were included in the RSS and the 'Scheme" data and model is not transferable to these products.<br>There are factors embedded in the RSS results, which are unique to the | Comments noted. |

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| | | products involved, dosage, frequency of administration, device, adherence etc, which may have an external impact on the outcomes associated with the scheme and should not be extrapolated across further products.<br>Plegridy and Extavia, should present their own evidence and be treated as independent products to avoid bias. Their merits or uncertainties should be establish within a stand-alone assessment. As mentioned above, Merck Serono believes, that beta-interferons could be considered as a class of products, but they are not identical and should not be assessed as such.<br>In terms of innovation, while it is true that Rebif has been available on the UK market since 1998, it has gone through enormous changes in relation to its delivery systems and support services. To directly support medicines optimisation, Merck Serono has produced an innovative electronic injectable-device which is intrinsically linked with the product and we would consider this a "step-change" in the management of the condition.<br>1. De Stefano N, Comi G, Kappos L, et al. J Neurol Neurosurg Psychiatry 2014;85:647–653. | |
| | MS society | *Would all people with CIS be expected to develop MS?*<br>- The results of numerous studies assessing the risk of conversion from CIS to clinically definitive MS, taken in combination, suggest that patients who have asymptomatic brain MRI lesions at the time of presentation of CIS have a 60% to 80% chance of developing CDMS by 10 years (Marcus et al, 2013) There are a number of people with CIS who go on to have no MRI evidence of MS and experience no further symptoms or episodes.<br>*Which technologies are used to treat CIS?*<br>- Currently beta interferons and glatiramer are licensed for CIS, the | Comments noted. |

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| | | ABN guidelines recommends that people diagnosed with CIS discuss the risk/benefits with their neurologist of taking a DMT. Due to the variation from people with diagnosed MS, CIS should receive its own STA for these treatments.<br><br>*Are there any other subgroups of people in whom beta interferon or glatiramer acetate are expected to be more clinically effective and cost effective or other groups that should be examined separately?*<br><br>There are a sub group of people who can develop an antibody that reduces the effectiveness of beta interferons. They could be considered as two sub populations for efficacy and cost effectiveness of interferons. | |
| | MS Trust | We do not think that CIS should be included in this appraisal. The scope of this appraisal is entirely to answer the question posed in the original TA32 and for which data has assiduously been collected over the past 10 years by MS centres and over 5,000 people with RRMS. The analytical model was tailored to this question and CIS was not in scope. Our view is that the licensing indications should continue to guide clinical use and reimbursement. We also recognise that there may be need for subsequent analysis regarding CIS.<br>Though we recognise that neither Extavia nor Plegridy were included in the RSS and associated data collection, our view is that they should both be included in this multi-technology appraisal.<br>Because of the unique nature of this multi-technology appraisal, it cannot be argued that any of these products represent an innovation or step-change in the management of RRMS. At the time of the original MTA, however, they certainly did. Re-appraisal of the original MTA with the benefit of long term data will provide a helpful benchmark in MS disease modifying drug therapy. | Comment noted. NICE has received a remit to appraise technologies for CIS. However, it is noted that there needs to be separate modelling considerations for CIS. For this reason the population with CIS has now been listed separately to the population with MS in the scope. |

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| | NHS England | *None to add* | Comment noted. |
| | Novartis | *Would all people with clinically isolated syndrome be expected to develop MS?*<br>We would anticipate 30-70% patients with CIS will develop MS (References: Miller et al. Lancet "Clinically isolated syndromes suggestive of multiple sclerosis, part I: natural history, pathogenesis, diagnosis, and prognosis" 2005; Kuhle et al. Multiple Sclerosis Journal "Conversion from clinically isolated syndrome to multiple sclerosis: A large multicentre study" 2015)<br><br>*Which technologies are used to treat clinically isolated syndrome?*<br>Extavia is licensed for patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis. | Comments noted. |
| | Royal College of Nursing | Please be aware that many people with MS have used these drugs with great effect. Many continue to do so and would choose an injectable that is safe over some of the newer drugs. We need to maintain choice for people. | Comments noted. |
| Additional comments on the draft scope | Biogen | Any additional comments on the draft scope<br><br>The commencement of the MTA and the end of the RSS overlaps. Is there guidance from NICE and the Department of Health on the timings of communications on the RSS? Additionally, how will data mining of the RSS by other interested parties be handled whilst the MTA is carried out?<br><br>Biogen would also like to understand the projected timings for the forthcoming | Comments noted. The Department of Health has agreed to share 10 year data from the RSS with NICE following sign off from its scientific advisory group. The timings of the review of natalizumab and |

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| | | MTA for natalizumab and fingolimod. It will be important that the second MTA is appropriately sequenced and timed following this MTA, to allow for a consistent approach and to take into account broader workload considerations. | fingolimod have not been determined. However, it is likely that a schedule will be agreed after the recommendations from the review of TA32 have been published. |
| | Health Improvement Scotland | The British Neurology guidelines included as first line therapy for relapsing remitting MS the following treatments: interferons, copaxone, teriflunamide and dymethyl-fumarate; from a clinical perspective, treatment in MS is rapidly evolving, and I presume that oral medications will be used more frequently in the following years; in the future, a new evaluation for both oral and classical modifying disease therapies in MS is clearly needed. | Comment noted. |
| | MS society | *Any additional comments on the draft scope*<br><br>The NICE Clinical Guideline for MS (CG186) should also be included in the list of related national policy. The revised (2015) prescribing guidelines for disease modifying therapy from the Association of British Neurologists should also be included - we would highlight a change in the treatment paradigm for RRMS, emphasising the importance of early treatment. This is reflected in the revised ABN guideline and has implications for the eligibility criteria for starting disease modifying treatment that currently apply. | Comment noted. CG 186 is listed under related NICE guidance. |
| | MS Trust | The NICE Clinical Guideline for MS (CG186) should also be included in the list of related national policy. The revised (2015) prescribing guidelines for disease modifying therapy from the Association of British Neurologists should also be included - we would highlight a change in the treatment paradigm for RRMS, emphasising the importance of early treatment. This is reflected in the revised ABN guideline and has implications for the eligibility criteria for | Comment noted. CG 186 is listed under related NICE guidance. For brevity, NICE scopes do not normally |

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| | | starting disease modifying treatment that currently apply.<br>Given the fact that NICE were involved in establishing the DH Risk-sharing Scheme and that substantial amounts of money and time (from clinicians, researchers and people with MS), have been spent reviewing the cost efficacy of these drugs over the last 10 plus years, it is essential that this appraisal is completed quickly following the conclusion of the RSS, using the resources already developed. | list clinical guidelines produced by other organisations. The ABN guidelines will, however, be discussed during the appraisal.<br><br>Comment noted. This appraisal has been timed to coincided with release of 10 year data from the RSS and the Department of Health and companies involved in the risk sharing scheme have agreed to share these data and the model with NICE to be used in this appraisal. |
| | NHS England | None to add | Comment noted. |
| | Novartis | No comments | Comment noted. |
| | Royal College of Nursing | See above comments | Comment noted. |

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| | UKMSSA | The ABN Revised guidelines for prescribing disease modifying treatments in MS emphasises the importance of early treatment and provides an overview of current treatment options that would inform this Appraisal. | Comment noted. |

**The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope**

Primary Care Neurology Society
The Royal College of Physicians have stated that it endorses the comments made by the Association of British Neurologists