NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Consideration of consultation responses on review proposal

Review of TA32; Multiple sclerosis - interferon beta and glatiramer acetate, TA127; Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis, and TA254; Fingolimod for the treatment of relapsing-remitting multiple sclerosis

The guidance was issued in:

TA32 – January 2002

TA127 – August 2007

TA254 – April 2012

The review date for TA127 had been set to coincide with the presentation of results from the SURPASS trial, which were anticipated in 2013. This study has now been terminated. The review of TA32 has previously been deferred and rescheduled to coincide with consideration of a review of TA127. A review decision on TA254 has also been scheduled to coincide with the review date of TA32.

Background

At the GE meeting of 16 April 2013 it was agreed we would consult on the review plans for this guidance. A four week consultation has been conducted with consultees and commentators and the responses are presented below.

Proposal put to consultees:	A combined review of TA32, TA127 and TA254 should be planned into the NICE work programme.
Rationale for selecting this proposal	Interferon beta and glatiramer acetate are currently provided in the NHS through the multiple sclerosis risk-sharing scheme. This was set up in 2002 and involves detailed monitoring of a cohort of patients to confirm the cost-effectiveness of these treatments. Preliminary data from the MS risk sharing scheme have already been published, and further data are likely to become available within the timeframe of a multiple technology appraisal. These data will be informative in estimating the clinical and cost effectiveness of the disease modifying drugs over several years. Furthermore, there are ongoing appraisals of four new drugs for the treatment of relapsing-remitting multiple sclerosis - alemtuzumab, dimethyl fumarate, laquinimod and teriflunomide – in which beta interferon, glatiramer acetate, fingolimod and natalizumab are indentified as comparators.

GE is asked to consider the original proposal in the light of the comments received from consultees and commentators, together with any responses from the appraisal team. It is asked to agree on the final course of action for the review.

Recommendation post consultation:	A combined review of TA32, TA127 and TA254 should be planned into the NICE work programme. The review should be scheduled to take place in 2015 to allow incorporation of mature data from the Risk Sharing Scheme.

Respondent	**Response to proposal**	**Details**	**Comment from Technology Appraisals**
Department of Health	No comment	The Department of Health will not be making any comments regarding the proposal to update the existing guidance for the above Health Technology Appraisal.	Comment noted.

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Bayer	Disagree (on the grounds of the timing of the review)	TA32 asked the Department of Health and National Assembly for Wales to consider if the medicines being appraised under TA32 could be made available in a cost effective manner and the multiple sclerosis risk share scheme (RSS) was established to fulfil this aim. Outcomes from year 6 of the RSS are expected during the timeline of the proposed review and a mechanism exists within the scheme to ensure that the medicines involved will be supplied to the NHS in a cost effective manner. It is therefore not a suitable juncture to conduct a NICE TA of these products – such a TA may risk NHS commissioners being provided with conflicting advice as to the clinical and cost-effectiveness, from two differing official sources.	Following consultation it is proposed that this review should be scheduled to allow the incorporation of mature data from the risk sharing scheme. These data are anticipated in late 2014 (see joint response from MS Trust / MS Society / Royal College of Nursing / UK MS Specialist Nurse Association / Association of British Neurologists).

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Bayer (continued)	Disagree (on the grounds of the timing of the review)	Were an appraisal to proceed that included evaluation of glatiramer acetate or interferon beta treatments for MS, then the only appropriate comparators would be natalizumab and fingolimod. However, as noted, both natalizumab and fingolimod have been appraised separately (TA127 and TA254) and are not proposed to be included in this review. Bayer shares many of the reservations raised by the MS Trust and MS Society in consultations of scopes for other planned TAs as to the inappropriateness of including `best supportive care' as a comparator in contemporary NICE appraisals. But without `best supportive care', natalizumab or fingolimod within the scope of the review, there remains no comparator treatment for appraisal and therefore no potential for altering the advice previously issued by NICE in TA32. There are currently four additional appraisals of products for the treatment of MS scheduled to be appraised by NICE. Bayer believe than rather conducting a review of these appraisals at the current time would not benefit the NHS, rather once the four additional appraisals have been conducted a treatment pathway for all the DMTs should be developed.	Comment noted. The appropriate comparators will be determined during scoping. The proposed review will include TA127 and TA 254 (therefore natalizumab and fingolimod will be included in the review). The review will be conducted after the outcome of the four STAs is known.

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Biogen Idec	Disagree (on the grounds of the timing of the review)	Biogen Idec notes the proposal to update a range of existing guidance referring to Multiple Sclerosis (MS) Disease Modifying Treatments (DMTs). Biogen Idec believes that the priority for the next 18 months should be clear clinical guidance on the use of both existing treatments and those that may become available over the next 12 months. Therefore we do not believe that an early review of the DMTs via an MTA would be beneficial for a number of reasons. **The Risk Share Scheme (RSS)** Funding of interferon beta and glatiramer acetate has been provided under the terms of the Risk Sharing Scheme (RSS). The RSS will provide an in depth analysis as to the cost effectiveness of the DMTs and the final results will be available in 2015. Publication of the final results from the RSS cohort will provide data that will be required for any new MTA and Biogen Idec believes that no assessment should start until this data is available. Any change in prices of these drugs resulting from the RSS results would have an impact on the cost effectiveness of all MS drugs and the outcome of any MTA.	Following consultation it is proposed that this review should be scheduled to allow the incorporation of mature data from the risk sharing scheme.

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Biogen Idec (continued)	Disagree (on the grounds of the timing of the review)	**New DMTs – licenced** Since the inception of the RSS both natalizumab and fingolimod have been launched in the UK and been assessed under the Single Technology Assessment (STA) process. This defines the circumstances in which they will be reimbursed and the populations considered cost effective for their use. Natalizumab is currently being reviewed by the EMA for a potential extension of its licence to a broader population and is also undergoing Phase III trials for use in SPMS populations. A review of natalizumab would not be appropriate until its use in these settings is confirmed. Fingolimod was assessed as recently as April 2012. In addition, the currently available treatments are recommended by NICE for different patient populations and therefore we are unclear as to the benefit of an MTA at this time. **New DMTs – in licencing process** Dimethyl fumarate, Teriflunomide, Laquinomod and Alemtuzumab are all new DMTs that are undergoing the EU licencing process and are expected to come to market within the next twelve months.	Comment noted. The NICE multiple technology appraisal process allows for consideration of different subgroups within the population with multiple sclerosis.

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Biogen Idec (continued)	Disagree (on the grounds of the timing of the review)	All these products are scheduled for STA by NICE and will therefore have clear guidance in place for their cost effective use in the NHS.	
		Biogen Idec believes there should be the opportunity for clinicians and patients to build experience of the use of these products in clinical practice before further guidance is developed.	See comments on proposed timing of the review above
		Clinical Guidelines	
		The treatment of MS is undergoing radical change with the available range of DMTs showing a marked expansion.	Comment noted. A review of NICE Clinical Guideline number 8 on management of multiple sclerosis in primary and secondary care is currently in progress.
		Biogen Idec would welcome new clinical guidelines on prescribing in MS which could be produced by a body such as the Association of British Neurologists (ABN)	
		Development of a consensus clinical treatment pathway, led by the ABN, would clarify and standardise clinical practice and inform future service needs to deliver this pathway.	
		Service development	
		With the move to MS being commissioned nationally as a specialized service, new service specifications are being introduced and time is required for these to be tested and implemented.	Comments noted. During the NICE technology appraisal process implementation is considered by the Appraisal Committee.

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Biogen Idec (continued)	Disagree (on the grounds of the timing of the review)	With the range of MS drugs that will soon be available a whole variety of settings for administration will exist from oral or self injection at home to infusion in hospital on an out patient or in patient basis. Furthermore dosage schedules may vary from daily, weekly, monthly to even annual or longer intervals All this means that services must be developed alongside guidance on cost and clinical effectiveness and guidance should not run ahead of service development. **CONCLUSION** Given the multiple reasons stated above Biogen Idec believes that an MTA of the selected products would be better suited at a time in the future when further data on the RSS and the use of new treatments due in the next 18 months is available. On this basis we believe guidance should not be reviewed until 2015.	Following consultation it is proposed that this review should be scheduled to allow the incorporation of mature data from the risk sharing scheme. These data are anticipated in late 2014 (see joint response from MS Trust / MS Society / Royal College of Nursing / UK MS Specialist Nurse Association / Association of British Neurologists).

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Merck Serono	Comments on timing on proposed MTA-Review	Merck Serono would like to take this opportunity to request some clarification around the number of appraisals pertaining to multiple sclerosis presently in development. Considering the products obtainable in the near future, we are unsure if an MTA at this time would provide a representative evaluation of treatment options for patients with relapsing-remitting multiple sclerosis. We would like to suggest that the timing of an MTA also consider the inclusion of the latest products already positioned within the NICE work stream. We see this as providing much needed clarity, reassurance and consistency of information within the NHS and to patients. This review could also have considerably implications for patients' and their treatment. Consequently, Merck Serono would like to raises some concerns relating to the data sources and the possible timings that might be considered. Within the request for information, we note that NICE refers to utilising data from the Risk-Sharing Scheme (RSS). While it is correct that some preliminary data is available and further data is due soon, this scheme is still too immature to generate definitive conclusions. The RSS was designed to run and gather data over a 10 year period*. Considering the inconclusive preliminary results available from the RSS, Merck Serono believes it would be inappropriate to base any evaluation on nascent data. For the RSS to provide a legitimate source of information in estimating cost-effectiveness of the products involved, Merck Serono would	Following consultation it is proposed that this review should be scheduled to allow the incorporation of mature data from the risk sharing scheme. During the single ongoing technology appraisals of alemtuzumab, laquinimod, teriflunomide and dimethyl fumarate for the treatment of relapsing-remitting multiple sclerosis the Appraisal Committee will propose a date when each technology should be considered for review.

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Merck Serono (continued)	Comments on timing on proposed MTA-Review	recommend that the setting of any assessment timeline should only include the complete 10 year RSS published data. In reply to NICE's request for information on timelines around on-going research, Merck Serono would like to draw attention to a large observational study. We consider this research integral for an assessment of products within the treatment of Multiple Sclerosis. This study was not included in the list of registered and unpublished trials provided by NICE. *"The Impact of Disease Modifying Therapies (DMTs) and Associated Support Services on Patient Reported Experience Measures (PREMs) and Outcomes (PROs) in Relapsing Multiple Sclerosis (RMS) Patients"* Study number EMR200136_550. The overall objective of this study is to establish the impact of current disease modifying therapies (DMTs) and associated support services on PREMs and PROs in relation to the treatment and management of RMS in the United Kingdom. This study will produce comparisons of Health-related quality of life (HRQoL) scores in patients receiving different treatments. It will also illustrate the impact of RMS on healthcare resources and work productivity in patients receiving DMTs. The expected conclusion date for this study is mid 2015 with published results available late 2015. Considering the significance of this information within an evaluation, Merck Serono would like to recommend that these results are available for review when NICE is considering the positioning of a Multiple Technology Appraisal (MTA) within its work stream.	Comments on on-going research noted.

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Merck Serono (continued)	Comments on timing on proposed MTA-Review	Merck Serono, understands and respects the need for NICE to review the current disease modifying therapies for the treatment of multiple sclerosis. However, we believe that the timing of this review is an important factor. As mentioned above we would like to suggest that this review take place, when the most valid and suitable data is available. Merck Serono considers that the most appropriate time for an MTA would be on completion of the RSS, the latest comparison data is available and when there is a better understanding of the treatment position of the latest products. We would be supportive of collaborating with NICE in their consideration of these matters.	Following consultation it is proposed that this review should be scheduled to allow the incorporation of mature data from the risk sharing scheme. These data are santicipated in late 2014 (see joint response from MS Trust / MS Society / Royal College of Nursing / UK MS Specialist Nurse Association / Association of British Neurologists)..
Novartis	Disagree (on the grounds of the timing of the review)	Novartis has no comments on the list of consultees and commentators for the proposed review. Novartis does have comments on the timelines for this review.	Following consultation it is proposed that this review should be scheduled to coincide with the publication of mature data from the risk sharing scheme. These data are anticipated in late 2014 (see joint response from MS Trust / MS Society / Royal College of Nursing / UK MS Specialist Nurse Association / Association of British Neurologists)..

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Novartis (continued)	Disagree (on the grounds of the timing of the review)	TA254 was only published in April 2012, with recommendations for further research. Understandably, there has not yet been time for these recommendations to be fully implemented. Furthermore, there is evidence that the guidance in TA254 has been implemented slowly and has not been incorporated into local formularies within the 90 day timeline required by the Department of Health (www.nice.org.uk). NICE is currently undertaking Single Technology Appraisals (STAs) for four new MS therapies and it would be helpful to include these therapies within the scope of an MTA to provide clarity on where to position all disease modifying therapies to support effective clinical practice and cost- effective treatment of MS. Therefore, Novartis proposes: • That the review should either continue in the short-term including only TA32 and TA127 and excluding TA254. • Alternatively, the review could commence from 2016 when it will be possible to include new information based on the research recommendations proposed in TA254. The later timeline would also offer a potential opportunity to review all MS therapies including those currently under consideration as STAs.	The comments on additional research conducted in light of research recommendations made in TA254 are noted. During a multiple technology appraisal manufacturers' are invited to submit information relevant to the appraisal. It is proposed that this review should be scheduled to commence after data from the Risk Sharing Scheme to mature, which may allow for more mature data to be presented from the Consultees studies to address research recommendations in TA254.

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Novartis (continued)	Disagree (on the grounds of the timing of the review)	No rationale has previously been provided for inclusion of TA254 within the proposed new review. In your letter of 25th April 2013, you state correctly that the final guidance for TA254 contained a recommendation that TA254 should be reviewed at the same time as TA32 and TA127. However TA254 offers no explanation for this recommendation except to state that that "The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators" (TA254 Section 8.1 p46). TA254 also offers recommendations for further research which include "the development of patient registries for multiple sclerosis to capture long-term treatment-related outcomes" and development of a new model for MS "ideally based on UK patient cohorts, which uses the best available evidence" (TA254, Section 6, p44). Novartis has studied carefully the recommendations for further research offered by NICE in TA254 and has undertaken a programme to develop data on long-term treatment-related outcomes in UK patient cohorts. Development of such data requires a medium to long-term timeframe of three to five years to ensure scientific validity is not compromised. Table 1 below outlines the primary and secondary objectives of studies currently underway to support NICE's research recommendations together with planned patient recruitment numbers and planned timings for first patient, first visit (FPFV) and for the clinical study report.	

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Novartis (continued)	Disagree (on the grounds of the timing of the review)	**Table 1 (supplied in confidence)** The second study in table 1 is an observational study focusing on real world evidence in a cohort of 400 UK patients; it has an end date of 2020 with recruitment closing in 2015. It is therefore anticipated the study will offer information on the full patient cohort through interim analysis by Q3 2016. Table 2 describes additional studies planned to commence in the UK, including a pregnancy registry and an observational study [redacted] **Table 2 (supplied in confidence)** Since the publication of TA254 in April 2012, additional information from only one further study has become available which could be considered if a review were to be undertaken including fingolimod within a 12 month timeframe. This study is described in Table 3 below: **Table 3 (supplied in confidence)** [redacted]	Tables are appended (commercial in confidence)

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Novartis (continued)	Disagree (on the grounds of the timing of the review)	In this context Novartis requests that if NICE commences its review in the short term it should focus only on TA32 and TA127, allowing Novartis time to collect the additional data which NICE has previously requested. Alternatively, NICE could postpone the review until 2016 when additional data requested by NICE will become available to assist in the evidence-based decision-making process for fingolimod. This later timeline would also offer the potential consideration to review all MS therapies including those currently under consideration as STAs.	

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Teva UK	Defer start of review	As Teva understands your letter, the proposal is to plan a combined review (i.e. MTA) of the above technology appraisals into the NICE work programme. Whilst we welcome a review of treatments which afford patients appropriate access to disease modifying therapies we would strongly argue that the timing and scope of the proposed review is not suitable, does not afford the greatest opportunity to clarify the clinical pathway for treatment of RRMS and risks creating an extended period of uncertainty for patients, prescribers and indeed payers. We recommend: 1. The Review of TA32 should only be 'activated' once final data emerges from the risk-sharing scheme. 2. A disease modifying treatment pathway for MS should be led Association of British Neurologists, with close involvement of the MS Trust and MS Society. This pathway should define starting, stopping, escalation and switching criteria. This should be completed before the review date proposed above. The development of a clear treatment pathway on the use of all disease modifying treatments for RRMS (this includes TA32, TA127 and TA254 plus any of the four drugs currently undergoing single technology appraisal: teriflunomide, dimethyl fumarate, laquinimod and alemtuzumab, which are determined to be cost-effective) would provide clarity for patients and prescribers.	Following consultation it is proposed that this review should be scheduled to allow the incorporation of mature data from the risk sharing scheme. These data are anticipated in late 2014 (see joint response from MS Trust / MS Society / Royal College of Nursing / UK MS Specialist Nurse Association / Association of British Neurologists). . Comment noted. A review of NICE Clinical Guideline number 8 on management of multiple sclerosis in primary and secondary care is currently in progress but does not include disease modifying drugs.

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Teva UK (continued)	Defer start of review	3. With the development of a treatment pathway, NICE should only seek to review these treatments as and when required. This should be entirely dependent upon whether there is evidence to warrant a reappraisal. A review of the technology appraisals of the DMTs, as required, along with the development of the treatment pathway by specialist MS neurologists and patient organisations, would be the preferred choice. An arbitrary combined review, which does not take into account all DMTs (including the four under ongoing Single Technology Appraisal) may only introduce unnecessary complexity and create a protracted period of uncertainty for patients, prescribers and payers.	Comments noted. All NICE review proposals are released for consultation. All NICE guidance and guidelines receive input from nominated clinical specialists and patient experts. Draft guidelines and guidance go for consultation by stakeholders which include professional and patient organisations.
		We also make the following comments/observations in support of our recommendations: • We are seriously concerned that a review of TA32 at this stage will act only to undermine the substantial investment and work done in the context of the RSS. As you know, a key concern at the time the RSS was established was the measurement of benefit over an appropriate time horizon. When the data from the RSS were analysed in 2009, the conclusions of the reviewers were that assessment was premature and that the data did not, at that stage, permit conclusions to be drawn. In these circumstances we strongly believe:	Comments and observations noted.

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Teva UK (continued)	Defer start of review	○ The data from products included in the RSS should not be analysed until they are mature enough to allow reliable conclusions to be drawn (i.e. at the end of the scheme) and ○ That further data from the RSS will ultimately support a review of the cost-effectiveness of the four treatments and that any review of TA32 at this stage (whether in the context of an expanded MTA or otherwise) will risk wasting the work done in the RSS to date. • The termination of the SURPASS trial as a trigger for the review of TA127 does not argue for initiating a review as consequently the incomplete study provides no new data to inform a review . • There are three anticipated developments which we believe should complete before undertaking an appraisal of the DMTs: ○ Single Technology Appraisal of four new DMTs for relapsing remitting MS (dimethyl fumarate, teriflunomide, laquinimod, alemtuzumab) will complete April 2014 ○ Publication of further data from the Risk Sharing Scheme (RSS) – End 2014 with Year 4 and 6 data available to the RSS Scientific Advisory Group in October 2013. The Year 8 and 10 data sets would be available to RSS Scientific Advisory Group Q3 2015.	

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Teva UK (continued)	Defer start of review	○ Publication of the revised NICE Clinical Guideline for the Management of MS (CG-8) – end 2014 Given the (planned) completion dates above, deferring consideration as to whether a review is necessary until late 2015 would be appropriate. • Awaiting the outcome of the update of the NICE Clinical Guideline for the Management of MS (CG-8), which will establish the current standard for MS services, will ensure that service costs included in the review reflect the latest recommended standards. This will have a direct bearing on the cost-effectiveness calculations for the DMTs. • A combined review will not provide clarity or consensus about the treatment pathway for RRMS. The various products identified by NICE have different indications and a combined appraisal, at this stage, will provide only limited assistance to the NHS in determining appropriate use of these medicines. MTAs are constrained by the available trial data and licensing indications, and may not resolve roadblocks or ensure consistency in clinical practice. Development of a consensus clinical treatment pathway, led by the ABN, would assist not only in clarifying and standardising clinical practice, but would also provide useful data regarding likely patient numbers within defined sub-groups, would provide insight as to how best to cluster the DMTs for review. Additionally, it would provide a framework into which drugs currently in development could be placed.	Comment noted. The purpose of a multiple technology appraisal is to assess whether each technology is a cost effective use of NHS resources rather than to define a treatment pathway.

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Teva UK (continued)	Defer start of review	• The introduction of four new DMTs offers additional choice, but also greater clinical complexity. Deferring a decision on a review until the end of 2014 will allow for the single appraisals to complete and the scope of a proposed review could be revised accordingly. • Development of a consensus clinical treatment pathway could be completed before the proposed date for reconsideration of a review (end 2014). A combined review would mean that some drugs which had just completed technology appraisal (teriflunomide or dimethyl fumarate for example), would then be re-appraised within a short time-frame. This inevitably calls into question the real value of an MTA in this context. With the development of a clear treatment pathway, reviews could be planned and undertaken as and when required, and the disruption and uncertainty for patients, prescribers (and indeed payers) would be minimised.	

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Teva UK (continued)	Defer start of review	** Teva also included some factual corrections to the original proposal paper* 1. **Section 4 Rationale** Furthermore, there are ongoing appraisals of four new drugs for the treatment of relapsing-remitting multiple sclerosis - alemtuzumab, dimethyl fumarate, laquinimod and teriflunomide – in which beta interferon, glatiramer acetate, fingolimod and natalizumab are indentified as comparators (fingolimod and natalizumab are not comparators for dimethyl fumarate) *The final scope for dimethyl fumarate did have fingolimod and natalizumab as comparators, the draft scope did not.* 2. **Section 7 Summary of evidence and implications for review** There are differences in the populations covered by the current marketing authorisations for fingolimod, natalizumab, interferon beta-1a and interferon beta-1b* *This sentence should also contain glatiramer acetate.* 3. *The Regard Study and Gala Study are not included in the evidence set under this heading and should be* 4. The BECOME study assessed interferon beta-1a compared with glatiramer acetate in 75 people over 2 years who had relapsing remitting multiple sclerosis or clinically isolated syndromes. *Should read The BECOME study assessed interferon beta-1b*	 Comment noted Comment noted Comment noted. It is anticipated that a systematic review carried out for the multiple technology appraisal will capture all relevant studies. Comment noted.

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Teva UK (continued)	Defer start of review	5. The BEYOND study compared 250 micrograms interferon beta-1b, 500 micrograms interferon beta-1b and glatiramer acetate	
		Should read 500 micrograms(unlicensed dose)	Comment noted
		6. CombiRx trial..... risk of relapse out come	
		Should note that the primary endpoint was reduction in annualized relapse rate not risk of relapse	Comment noted

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Multiple Sclerosis Trust Multiple Sclerosis Society Royal College of Nursing United Kingdom Multiple Sclerosis Specialist Nurse Association Association of British Neurologists	No (defer decision to review)	As we understand your letter, the proposal is to plan a combined review (i.e. MTA) of the above technology appraisals into the NICE work programme. We welcome a review of treatments for disease modifying therapies (DMTs), but we would strongly argue that the timing and scope of the proposed review is not suitable, does not afford the greatest opportunity to clarify the clinical pathway for treatment of RRMS, and risks creating an extended period of uncertainty for patients and prescribers. We recommend:- 1. The decision to review the guidance should be deferred to late 2014. 2. The development of a clear treatment pathway on the use of all licensed DMTs for RRMS including the four drugs currently undergoing single technology appraisal: teriflunomide, dimethyl fumarate, laquinimod and alemtuzumab. The Association of British Neurologists, working with the MS Trust and MS Society and the UK MS Specialist Nurse Association, would be happy to develop such a pathway, to be completed before the review date proposed above. The pathway would assist in clarifying and standardizing clinical practice; provide useful data regarding likely patient numbers within defined sub-groups, and thus scale to the different DMTs; and provide a framework into which drugs currently in development could be placed. 3. With the development of a treatment pathway, NICE might then seek to review these treatments as and when new evidence warrants such reappraisal.	Following consultation it is proposed that this review should be scheduled to allow the incorporation of mature data from the risk sharing scheme. These data are anticipated in late 2014 (see joint response from MS Trust / MS Society / Royal College of Nursing / UK MS Specialist Nurse Association / Association of British Neurologists). The comments on needing to clarify the clinical pathway are noted. The purpose of a multiple technology appraisal is to assess whether each technology is a cost effective use of NHS resources rather than to define a treatment pathway- which would be the purpose of a clinical guideline. Following the maturation of the risk sharing scheme it is imperative NICE issues timely guidance on whether interferon beta, glatiramer acetate, fingolimod and natalizumab are a cost effective use of NHS resources.

Respondent	Response to proposal	Details	Comment from Technology Appraisals
MS Trust / MS Society / RCN / UK MS Specialist Nurse Association / ABN (continued)	No (defer decision to review)	We also make the following comments in support of our recommendations:- • The termination of the SURPASS trial as a trigger for the review of TA127 (mentioned in your letter) does not argue for initiating a review now, as the practical consequence of the termination is that no new data will be emerging. • There are three anticipated developments which we believe should complete before undertaking an appraisal of the DMTs: o Publication of further data from the Risk Sharing Scheme (late 2014). This will support a review of the cost-effectiveness of the four drugs (considered not cost-effective in TA32). It would be premature to begin the currently proposed review of these same drugs without the benefit of these data, which could trigger price adjustments that in turn could have a significant impact on a future review. A review could also threaten final data collection. o Publication of the revised NICE Clinical Guideline for the Management of MS (CG-8) – end 2014. This will establish the current standard for MS services, and ensure that service costs included in the review reflect the latest recommended standards, so having direct bearing on the cost-effectiveness calculations for the DMTs.	Comments noted

Respondent	Response to proposal	Details	Comment from Technology Appraisals
MS Trust / MS Society / RCN / UK MS Specialist Nurse Association / ABN (continued)	No (defer decision to review)	○ Single Technology Appraisal of four new DMTs for relapsing remitting MS (dimethyl fumarate, teriflunomide, laquinimod, alemtuzumab) – mid-2014. The potential introduction of four new DMTs offers additional choice, but also greater clinical complexity. Deferring a decision on a review until the end of 2014 will allow for the single appraisals to complete; and the scope of a proposed review could be revised accordingly Given the (planned) completion dates above, deferring consideration as to whether a review is necessary until late 2014 would be appropriate.	Following consultation it is proposed that this review should be scheduled to allow the incorporation of mature data from the risk sharing scheme. These data are anticipated in late 2014
United Kingdom Multiple Sclerosis Specialist Nurse Association (2)	Defer start of review	Having analysed the proposed scoping exercise and the responses drafted by both MS Society and MS Trust in conjunction with the association of British Neurologists, the UKMSSNA would entirely agree with the joint responses produced. We also believe that a delay of the MTA until late 2014 will be beneficial and support the idea that the use of best supportive care would not be beneficial in this instance. The UKMSSNA would add their voice in support of the MS Specialist Nurses of the UK to spearheading the proposed pathway led by the ABN as key players in that pathway; involved in advising, training and monitoring of all people with MS on disease modifying therapies.	Following consultation it is proposed that this review should be scheduled to allow the incorporation of mature data from the risk sharing scheme. These data are anticipated in late 2014 (see joint response from MS Trust / MS Society / Royal College of Nursing / UK MS Specialist Nurse Association / Association of British Neurologists).

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Royal College of Nursing (2)	No (defer decision to review)	The Royal College of Nursing would like to refer NICE to the collaborative response being submitted by the MS Trust, The MS Society and the Association of British Neurologists. We agree with them that the timing of and scope of the proposed review is not suitable and that a review would not be beneficial at this stage. We consider that deferring any decision to undertake this review until the single appraisals and the outcomes of the other work identified in the paper have been completed would provide valuable information which would inform the need and scope for the appraisal.	Following consultation it is proposed that this review should be scheduled to allow the incorporation of mature data from the risk sharing scheme. These data are anticipated in late 2014 (see joint response from MS Trust / MS Society / Royal College of Nursing / UK MS Specialist Nurse Association / Association of British Neurologists).
Association of British Neurologists (2)	Defer start of review	The ABN agrees that a combined re-review of the products mentioned is indeed appropriate, as you suggest. Given that new data from the DoH MS Treatment Risk Sharing Scheme will not emerge before the spring of 2014 (at the earliest), we suggest it would be appropriate to defer the proposed re-review until then. Also, since NICE is currently conducting Technology Appraisals of four other separate MS products, we suggest that it would again be sensible for this proposed re-review to be deferred until these appraisals have all been completed.	Following consultation it is proposed that this review should be scheduled to allow the incorporation of mature data from the risk sharing scheme. These data are anticipated in late 2014 (see joint response from MS Trust / MS Society / Royal College of Nursing / UK MS Specialist Nurse Association / Association of British Neurologists).

No response received from:

Patient/carer groups	General
• Afiya Trust • Black Health Agency • Brain and Spine Foundation	• Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary

• Disability Rights UK • Equalities National Council • Independent Age • Leonard Cheshire Disability • Multiple Sclerosis National Therapy Centres • Multiple Sclerosis Resource Centre • Muslim Council of Britain • Muslim Health Network • Neurological Alliance • South Asian Health Foundation • Specialised Healthcare Alliance <u>Professional groups</u> • British Association for Services to the Elderly • British Geriatrics Society • British Neuropathological Society • British Society of Rehabilitation Medicine • Chartered Society of Physiotherapy • Institute of Neurology • Neurosupport • Primary Care Neurology Society • Royal College of General Practitioners • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • Therapists in MS • United Kingdom Clinical Pharmacy Association <u>Others</u> • Department of Health	• Care Quality Commission • Commissioning Support Appraisals Service • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • Multiple Sclerosis Society Wales • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Public Health Wales NHS Trust • Scottish Medicines Consortium • Wales Neurological Alliance <u>Comparator manufacturers</u> • None <u>Relevant research groups</u> • British Neurological Research Trust • Health Research Authority • MRC Clinical Trials Unit • National Institute for Health Research • Research Institute for the Care of Older People <u>Assessment Group</u> • Assessment Group tbc • National Institute for Health Research Health Technology Assessment Programme <u>Associated Guideline Groups</u>

• NHS England • NHS Norwich CCG • NHS Wirral CCG • Welsh Government	• National Clinical Guidelines Centre <u>Associated Public Health Groups</u> • None

GE paper sign-off: Janet Robertson, Associate Director – Technology Appraisals Programme

Contributors to this paper:

Technical Lead: Mary Hughes

Project Manager: Andrew Kenyon

10 June 2013