Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Decisional Dilemmas in Discontinuing Prolonged Disease-Modifying Treatment for Multiple Sclerosis*

Draft review available for public comment from October 14, 2014 to November 10, 2014.

Research Review Citation: Butler M, Forte ML, Schwehr N, Carpenter A, Kane RL. Decisional Dilemmas in Discontinuing Prolonged Disease-Modifying Treatment for Multiple Sclerosis. Comparative Effectiveness Review No. 150. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2012-00016-I.) AHRQ Publication No. 15-EHC012-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2015. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each research review is posted to the EHC Program Web site in draft form for public comment for a 4-week period. Comments can be submitted via the EHC Program Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Supplemental material provided by peer and public reviewers as letters and exhibits are available for viewing in the supplement document accompanying this report of disposition of comments.

Commentator & Affiliation	Section	Comment	Response
Peer/TEP Review Section			
TEP Reviewer #1	Introduction	Well done and organized. Sets out the key questions clearly and succinctly. I think however the conceptual model (page ES-4) misses a critical element for discontinuation which is the following components: tolerability of the medication, disease characteristics at the time of discontinuation (relapses, progression, MRI activity), risk on ongoing disease treatment, other impediments to continued medication use (e.g. difficulty of obtaining, injecting or ingesting, cost, etc.)	The elements mentioned are critical clinical elements and are important to note. The model depicts the context within which clinical decisions are made. The figure has been left unrevised (the clinical elements can be inferred from the "knowledge" component and the area of overlap between the physician and patient). The clinical elements noted by the reviewer have been added to the text describing the figure.
TEP Reviewer #2	Introduction	Clearly written albeit an abbreviated explanation of the techniques used would have provided this reviewer with a better understanding of this approach	Thank you for the comment. The methods are provided in detail in the Methods section of the report.
Peer Reviewer #3	Introduction	PRMS is progressive relapsing, not primary relapsing	Thank you, this has been corrected.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Introduction	the section on “Clinically definite MS types” is problematic. Most importantly, it should be acknowledged that many patients fit into more than one phenotype described, and that these phenotypes are imperfect and likely a spectrum over overlapping syndromes. Furthermore, there are problems with their descriptions in the text. Authors should review seminal papers by Lublin et al on the topic and improve this section Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology. 1996 Apr;46(4):907-11. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, Wolinsky JS, Balcer LJ, Banwell B, Barkhof F, Bebo B Jr, Calabresi PA, Clanet M, Comi G, Fox RJ, Freedman MS, Goodman AD, Inglese M, Kappos L, Kieseier BC, Lincoln JA, Lubetzki C, Miller AE, Montalban X, O’Connor PW, Petkau J, Pozzilli C, Rudick RA, Sormani MP, Stüve O, Waubant E, Polman CH. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 2014 Jul 15;83(3):278-86. Doi: 10.1212/WNL.0000000000000560. Epub 2014 May 28	Minor revisions to the descriptions have been made and the Lublin et al. 2014 article cited.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Introduction	"People taking natalizumab may take a drug holiday or discontinue use completely if their risk factor increases assessed by a positive test for the anti-JCV antibody status." This statement has grammatical problems. In addition, a decision regarding Tysabri depends on a risk benefit discussion between patients and physicians. Many JCV+ patients at high risk for PML elect to stay on this medication due to efficacy, lack of better options, or their assessment of risk. Not all patients discontinue at certain defined risk. I know of no data that "drug holidays" decrease risk, nor is this common practice, and any mention of such should include citations.	The sentence grammar has been corrected. The sentence itself does not imply that a drug holiday decreases risk, rather simply that a drug holiday (or final discontinuation) may be the decision if there is an increase in risk factors. Neither a specific defined risk level nor prescribed clinical practice was provided.
Peer Reviewer #4	Introduction	"Women must weigh the possible risks of DMT exposure to the unborn fetus against the maternal risk of disease progression if she discontinues DMT." There is literature on such, particularly DMT in pregnancy, and this should be reviewed and cited here. Some is mentioned later in the report.	As this is a systematic review, review of the literature is in the results section. A sentence was added to clarify that no FDA-approved drug is labeled as Class A (safe for use in pregnancy).
Peer Reviewer #4	Introduction	"Neurologists commonly counsel a woman to discontinue her medications 3 months prior to trying to conceive," there should be a citation here, or if this is anecdotal, a range is more appropriate, most MS specialists I know counsel one month. Perhaps "1-3 months" should be written.	Thank you for the comment. The sentence regarding the stopping period was removed and the paragraph revised to point out the decisions facing the MS patient and her physician.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Introduction	"Such a point may be reached when a person is determined to be nonresponsive to the medication due to disease progression." These medications were developed, and clinical trials powered, to show that they prevent relapses, and radiographic evidence of inflammation, not neurodegeneration. Thus absence of relapse and MRI changes in the presence of progression does not necessarily indicate "nonresponse". There is much debate in the MS scientific community on the degree, if any, of relationship between neurodegeneration (which causes "progression") and inflammation in MS, and a more nuanced discussion of this is needed in this text.	The paragraph did not define "nonresponse" nor mention neurodegeneration or inflammation. Nonresponse was discussed within the context of prolonged used of DMTs (longer than the 2-3 years followed in the clinical trials mentioned by the reviewer). The paragraph did acknowledge the uncertainty of determining when a patient is nonresponsive after prolonged treatment. However, the paragraph did undergo some revision.
Peer Reviewer #4	Introduction	"MRI to identify multiple sclerosis-related lesions has been shown to correlate with short-term relapse rates, 6 months to 2 years." The below study should be reviewed and referenced as well as additional work by Sormani in this area. Sormani MP, Bruzzi P. MRI lesions as a surrogate for relapses in multiple sclerosis: a meta-analysis of randomized trials. Lancet Neurol. 2013 Jul;12(7):669-76. Doi: 10.1016/S1474-4422(13)70103-0. Epub 2013 Jun 3. Review.	The Sormani article has been added as a reference to the paragraph.
Peer Reviewer #5	Introduction	Clear, concise, accurate, well written.	Thank you for the comment
Peer Reviewer #6	Introduction	Few or no Neurologists stop MS drugs for 3 months before pregnancy; this would be quite dangerous, and a significant number of patients would have iatrogenic exacerbations.	Thank you for the comment. A sentence was added to clarify that no FDA-approved drug is labeled as Class A (safe for use in pregnancy), the sentence regarding the stopping period was removed, and the paragraph revised to point out the decisions facing the MS patient and her physician.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Introduction	Cochrane data that are cited suffer from the same drawbacks, attributing significance to the obvious, and lacking clinical insight. Also flawed, on page 9 (and again on page 10) the Cochrane inappropriately ranks drugs based on efficacy in mismatched trial populations, on an outcome measure that does not significantly affect long-term disability or death.	This Cochrane review followed the methods established by the Cochrane Collaboration for reviews and overviews of reviews.
TEP Reviewer #7	Introduction	I thought the key questions were appropriate as were the methods but was concerned about the negative tone of the conclusions.	Thank you for the feedback. We have revised the report to provide a more positive tone.
TEP Reviewer #8	Introduction	It is progressive-relapsing MS not primary relapsing. Description of the condition is oK	This has been corrected.
TEP Reviewer #9	Introduction	I found the review to have been well executed and to have followed all of the basic aspects and methods expected in a systematic review, and the authors go beyond this by also including a well-articulated conceptual framework which guides the review and also transparently communicates its underlying assumptions. This framework may be challenged by the MS community but I feel that it is a strength to have it included.	Thank you for the comment.
TEP Reviewer #1	Methods	Inclusion and exclusions justifiable and logical. I cannot comment on the statistics as I have no expertise in this area.	Thank you for the comment.
TEP Reviewer #2	Methods	Inclusion and exclusion criteria are clearly stated and justifiable. Search strategies are fairly clear albeit I don't know the exact meaning of "7 articles were found by hand search" is (page 12 line 10 or 11)	Thank you for the comment. "Handsearching" is a term used in systematic review methodology that refers to locating articles missed by algorithms written to search electronic databases.
Peer Reviewer #3	Methods	I have no concern about the methods	Thank you for the comment.
Peer Reviewer #4	Methods	appropriate	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Methods	Logical; mixed qualitative and quantitative; but, appropriate so given the topic covered and the literature survey/summary.	Thank you for the comment.
Peer Reviewer #6	Methods	Methods are weak or not detailed—ibid.	Detailed methods are provided in the methods section of the full report. The evidence report utilizes methods developed by AHRQ EPC program in collaboration with several experts. They are consistent with other established methods such as those by Cochrane and IOM
Peer Reviewer #6	Methods	On p 14, 15 level of evidence ... is vague, even though they are the cornerstones of many analyses.	This review does not use levels of evidence as a classification method. AHRQ methods involve grading the strength of the evidence through examining study limitations not just by study design category but also by study conduct. AHRQ's method of grading evidence is consistent with the GRADE approach.
TEP Reviewer #7	Methods	Although the inclusion of only studies of 3 years or more is defensible, the result is that important information concerning the positive effects of treatment was not included. The search strategies were appropriate as were the analytic methods.	Thank you for the comment. The information of positive effects was included in the introduction section with the discussion of the Cochrane review of the 2-3 year clinical trial research.
TEP Reviewer #8	Methods	Yes	Thank you for the comment.
TEP Reviewer #9	Methods	I agree with the authors that due to differences in design and outcomes it is impossible to perform meta-analyses of pooled outcomes, however in limited applications this has been successfully done (such as some published studies comparing interferon outcomes). While the report could be criticized for not conducting meta-analyses where possible, I think it is defensible here because they could not be done systematically across treatments and for all outcomes.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
TEP Review #9	Methods	The only area where I feel that the review will garner criticism and debate will be in the inclusion and exclusion of particular studies. Following the selection criteria and rationale, study inclusion appears appropriate, however many trials that are currently considered to be "pivotal" or foundational studies by the MS community (e.g. the Panitch BENEFIT trial, and others) were excluded. This may lead critics to argue that the systematic review was too narrowly focused or did not include all relevant evidence. However, in any systematic review it is virtually impossible to satisfy all readers in this aspect. I expect significant discourse and debate to occur in this area as a result of this publication- and I see this as a benefit rather than a detractor.	Thank you for the comment.
TEP Reviewer #1	Results	I can't imagine reading this entire report for content. I think at most an executive summary will be read, and the body of this should be available for those who need fine grain detail (for example, as a base for planning studies).	Thank you for the comment. The publication is structured as a shorter executive summary and a more complete and detailed report with supporting appendixes.
TEP Reviewer #2	Results	The results are well presented. The publication would take a very long time to review and digest. It is a wonderful resource for highly interested parties. It is overpowering to a clinician with limited ability and time to review. Because of the latter, I feel it will be of little use to the MS practitioner. In my general statements I have already suggested one of what I think is a key omission in the determination of why DMTs are continued in SPMS. (see above)	Thank you for the comment.
Peer Reviewer #3	Results	I have no concern about the results	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	the paper by Shirani et al 2012 is relied upon heavily within this report. Authors should review, cite, and consider incorporating critique of this data published below Interferon Beta Use and Disability Prevention in Relapsing-Remitting Multiple Sclerosis Benjamin M. Greenberg, MD, MHS; Laura Balcer, MD; Peter A. Calabresi, MD; Bruce Cree, MD, PhD; Anne Cross, MD; Teresa Frohman, PA-C; Ralf Gold, MD; Eva Havrdova, MD, PhD; Bernhard Hemmer, MD; Bernd C. Kieseier, MD; Robert Lisak, MD; Aaron Miller, MD; Michael K. Racke, MD; Lawrence Steinman, MD; Olaf Stuve, MD, PhD; Heinz Wiendl, MD; Elliot Frohman, MD, PhD JAMA Neurol. 2013;70(2):248-251. Doi:10.1001/jamaneurol.2013.1017.	Thank you for the suggestion. We have not cited this particular paper as there was a considerable conversation carried out in the journal commentary and letters. The Shirani paper appears heavily relied on because of the limited studies with acceptable risk of bias. However, the findings based on the Shirani article was rated as low strength of evidence due to the kinds of challenges as this suggested reference cites.
Peer Reviewer #5	Results	The detail was comprehensive yet well focused. Are the characteristics of the studies clearly described? YES Are the key messages explicit and applicable? YES Are figures, tables and appendices adequate and descriptive? YES	Thank you for the comments.
Peer Reviewer #5	Results	There is a GARY BIRNBAUM, M.D poster from AAN (2014) that is particularly pertinent (but only a poster and lecture and not publication). His was a study on stopping MS drugs.	Thank you for the suggestion. This review included only published literature. Poster presentations rarely have the detail necessary to fully review a study.
Peer Reviewer #6	Results	interpretations are flawed	We believe the interpretations are sound and reasonable.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Results	There is serious lack of rigor in describing the 21-y long-term follow-up of the pivotal Betaseron trial. The evidence was not "low strength" — the paper was called the most important MS paper of the year by several sources. Including the AAN. Goodin, Reder, et al., Neurology 2012 was very well-controlled and had >98% ascertainment. How was this moderate risk of bias? (How is this defined...?) The level of evidence applied by the Neurology statistician was clearly wrong, as argued in Goodin n Reder MS jnl, 2012. The placebo-controlled trial lasted 5 years, not 2, before the next 16 years of follow-up in the long-term study, again calling into question the level of scrutiny applied to any of the articles reviewed by the authors of the present position paper.	The Methods section provides detail regarding strength of evidence and risk of bias assessments, and the tool used to assess risk of bias was provided in the Appendix. The study was assigned a moderate risk of bias in large part because exposure to competing interventions during the prolonged follow-up were not described or included in the analysis. The study was a well-conducted one, on a difficult research question. But without accounting for the other competing influences, other plausible confounding factors/counterfactual arguments cannot be ruled out. Given this risk of bias for a single study contributing to the body of the evidence, we believe a low strength evidence is appropriate. The possibility that future research may change the results remains a real possibility.
Peer Reviewer #6	Results	Shirani et al, , JAMA, 2012, in contrast, was highly biased—as detailed in two letters (Goodin, Reder, Cutter JAMA, 2012 and Greenberg et al., JAMA Neurology, 2013). Briefly, the sickest patients were treated, those with mild MS were not. Also, those in the untreated group who had attacks or progression (i.e., worse prognosis) were put on therapy and were then removed from the untreated group. There were even more concerns listed in the letters.	The potential limitation of sample selection was noted and taken into account in the risk of bias assessment. Again, low strength of evidence communicates the possibility that future research may change the results.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #7	Results	I thought that the report underemphasized the implications of some studies, such as adherence studies which demonstrated the negative effects of discontinuing treatment. Although these were not the gold-standard controlled trial, I thought that the evidence they provide is too important to overlook. The presentation was appropriate although I would have liked to see more information about the results of the studies reviewed as opposed to the characteristics of those studies.	Thank you for the suggestion. We did discuss the limitations of including adherence articles when the indexing of articles addressing preferences is not well indexed in electronic databases. Adherence literature as a body, however, addresses barriers to achieving an agreed-upon treatment plan, which is a fundamentally different issue than when a physician and patient consider whether discontinuing is appropriate considering the patient's current situation.
TEP Reviewer #8	Results	Yes. I would have preferred a list of utility scores corresponding to the health states assessed in the studies described in KQ2. Easy enough to pull the references though.	We did not report the utility scores themselves as they were not informative for the key question.
TEP Reviewer #1	Discussion	Summary tables should reference the specific articles on which the table is based. I think many will go directly to these summary tables for their data.	We have adopted the suggestion.
TEP Reviewer #2	Discussion	The conclusions are clearly stated, but of limited practical value. The future research section is clear, but not easily translated into new research.	Thank you for the comment.
Peer Reviewer #3	Discussion	Yes	Thank you for the comment.
Peer Reviewer #4	Discussion	MS therapeutics represents a global market approaching 16 billion dollars a year, medications cost $60,000/yr in the US. As much as possible, payment for these medications should be tied to evidence for long term efficacy and/or disability prevention, the pharmaceutical companies should be incentivized to conduct longitudinal studies.	Thank you for the comment.
Peer Reviewer #5	Discussion	Implication is clear: Specific studies on stopping MS drugs and the implications / results of doing so is sorely needed. As there is little specific published research on this topic. Yes to all of the above.	Thank you for the comment.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Discussion	Everything is clearly stated, but that is not sufficient.	Thank you for the comment.
TEP Reviewer #7	Discussion	The report appropriately emphasized the need for more controlled studies of a long-term nature. However there should have been more emphasis on the fact that in the absence of evidence to the contrary, treatment should be continued unless there are serious side effects or deterioration of symptoms.	Thank you for the comment. The report introduction and discussion have been revised to highlight the review is relevant for people with MS who have used DMTs for a prolonged period of time and for whom there is suspicion that treatment is no longer helping.
TEP Reviewer #8	Discussion	Yes to all, The research studies described will be difficult to do but lesser studies will be uninformative.	Thank you for the comment.
TEP Reviewer #9	Discussion	The methods and findings of the review appear to lend appropriately to recommendations for future research and dialogue.	Thank you for the comment.
TEP Reviewer #9	Discussion	One way to address this [potential funding] problem is highlighted in the final section of the report, which I am delighted to see focuses on decision making and introduces the concepts of decision analysis shared decision making (SDM). I think the report could perhaps have gone further to classify disease modifying treatment as a preference sensitive rather than effective care decision, but this is a topic open to further study and debate. The fact that SDM is even mentioned and highlighted in this report brings the field into an entirely new domain that has been leveraged by other fields but not yet by MS. I feel that part of the solution to the current dilemma of disease modifying treatment in MS may be through SDM and that through SDM we may be able to avoid black and white policy determinations about disease modifying therapy use and coverage. For example, one future policy solution may be to require SDM in disease modifying treatment decisions.	Thank you for the comment. We have added opening text to the Discussion section to firmly ground the review in the context of MS patients who have followed a prolonged DMT treatment plan and are entering a decisionmaking process with their providers regarding the appropriateness of discontinuing treatment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #9	Discussion	Finally, I feel that the report could have gone further to include some discussion of the necessary contributions of systems level factors to disease modifying therapy treatment selection and adherence, and to the successful implementation of SDM. Areas such as implementation science and quality improvement, which combined are often referred to as healthcare improvement science, should be included in the future of MS research and the improvement of MS treatment decision and outcomes. However, in this case, I understand that there is currently no literature in MS to review, which certainly makes it difficult to include in a systematic review article.	Thank you for the comment. We have added text to the Future Research section suggesting that efforts in healthcare improvement science would be an important element in supporting treatment decisions for MS patients.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	General Comments	A review of the evidence surrounding discontinuation of DMTs is timely, important in terms of cost and patient care. This report is voluminous, careful, and well organized. Unfortunately, the literature it reviews is not. At the end of the day, there is little or no guidance on the core questions which were: who should continue on DMTs and who should stop, when do patients stop benefiting from DMTs. This does deal with the issue of discontinuation of natalizumab and switching to other agents but again the literature is very limited and does not give much guidance to the clinician. I think the major benefit of this report would be if it proposed specific studies that should be done and study designs that might provide firmer answers on what to do. The impact is potentially large as there is a large cohort of MS patients on very expensive medication. If a large subset of these patients really don't need these medicines, or are taking unnecessary risks, we should have guidance as to when to avoid these medications. The recent case with PML occurring after 4 years on tecfidera reinforces that even the most 'benign' appearing of our medicines has long term risks.	Thank you for the comment. While providing suggestions for future research is a standard section in AHRQ EPC reports, we leave the proposal and design of specific studies to funders and researchers in the field. Dimethyl fumarate (Tecfidera) was eligible for inclusion, but no long-term studies were reported. The reviewer's point is well-taken, though, and the newly released information was incorporated into a new paragraph on harms in the discussion section
TEP Reviewer #1	General Comments	Well structured. Probably could be less wordy overall, but the structure guides the reader to critical elements clearly.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	General Comments	The report is technically well done, but suffers from the lack of definitive studies with which to draw clinically meaningful conclusions. Key questions are identified and the methods are clear. I did feel that studies using interferonB-ib and interferonB-1a in SPMS could have pointed to class III evidence that in SPMS (especially early SPMS) relapses and MRI scan changes are positively affected and that this provides a rational expectation that longer studies may have shown a clinical effect upon disability provided patients stayed on therapy. I am not sure that patient preferences can be so easily dismissed. I suspect that given the side effects of some of the products and the high discontinuation rates in early treatment, that the tendency for some patients to continue therapy may be based upon clinical benefits that are not currently obvious or measurable.	Thank you for the comment. The review scope was limited to long-term studies of DMT. The reviewer points out a possible source of information for SPMS patients use of DMT. However, should such evidence become available and DMTs were used for prolonged treatment plans, such patients would inevitably face the same decisional dilemma regarding treatment discontinuation.
TEP Reviewer #2	General Comments	As stated the non-definitive nature of the available information makes future policy very murky. There are enough inconclusive data in this report that it may well be used to form any policy that favors any specific stake holder's bias.	We share the concern that people do occasionally use information, or the lack thereof, inappropriately, often to forward their own agendas. Inconclusive data is not a sufficient end-point on which to base permanent policy. This report is relevant for MS patients who have used DMTs for a prolonged treatment plan. These patients, and their providers, have to make decisions based substantially on their clinical and personal experience until such time the evidence base can better inform their decisions.
Peer Reviewer #3	General Comments	Clinically meaningful – yes. Key questions appropriate and states – yes. Clarity and usability – yes.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	General Comments	The report is very clinically meaningful. This question and the lack of data for "evidenced based" decisions is a particular problem in the field of multiple sclerosis. The key questions are appropriate, as an MS specialist I am quite familiar with the lack of rigorous data on this topic.	Thank you for the comment.
Peer Reviewer #5	General Comments	The report is long overdue and absolutely needed. It is clinically essential (not just meaningful). Key questions are clear and appropriate.	Thank you for the comment.
Peer Reviewer #5	General Comments	Clarity and Usability: Yes to all of the above.	Thank you for the comment.
Peer Reviewer #6	General Comments	This review is welcome because this issue is important, MS drugs are expensive, and there is no consensus among Neurologists on best therapy, or definition of failure. The Conclusions on page 5 are appropriate.	Thank you for the comment.
Peer Reviewer #6	General Comments	However, the analysis is harmed by the authors' unfamiliarity with MS, and poor review by an anonymous panel of Neurologists with questionable expertise in MS. Errors like relapse-remitting (relapsing) and primary relapsing (progressive relapsing) MS could be forgiven. But, that DMDs are "not for life-long use" is wrong, and without clinical insight. Only one DMD is mentioned on the page 5 abstract.	The purpose for posting the draft is for comments on the accuracy of the evidence, which should stand on its own. Therefore, the names of individuals are redacted from the draft. Authors, TEP, and KI information will be provided in the published report, according to AHRQ process. We have revised the language regarding the intended period of use of DMTs so that the report, and readers, remain focused on the continuing decisional dilemma of when discontinuing treatment is appropriate for MS patients with prolonged DMT treatment plans.
Peer Reviewer #6	General Comments	Assumptions ab initio are not solid, calling into question the entire effort.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #7	General Comments	The report is clinically meaningful but errs too much in emphasizing the lack of evidence for benefits. This emphasis could potentially lead to increasing inappropriate cessation of treatment because readers may interpret the report's conclusions as meaning that there is no value in continuation. In reality the report indicated a relative lack of evidence for continuation. I thought that the target population and audience were appropriately defined and the key questions appropriate and explicitly stated.	Thank you for the comment. We have revised the report to emphasize the review is intended to address the question of information to support decisionmaking for providers and MS patients who, after prolonged use of DMTs, may need to consider when it is appropriate to discontinue because the drug is no longer helpful.
TEP Reviewer #7	General Comments	I thought the organization was excellent and the findings clearly presented and summarized.	Thank you for the comment.
TEP Reviewer #8	General Comments	Yes, it was clinically meaningful. The limitations to the clinical applicability are related to the limitations in the evidence, not the quality of the review.	Thank you for the comment.
TEP Reviewer #8	General Comments	A little disappointed that switching was beyond the scope.	We understand the disappointment. There are always important questions that must be left to another endeavor.
TEP Reviewer #8	General Comments	Also, the preferences evidence seemed applicable to MS in general, not just discontinuation. Was any preference evidence excluded if it did not deal with discontinuation. (It does not seem so, from the studies—this is a plus).	It may indeed be true that the preference information can be informative beyond the immediate research questions.
TEP Reviewer #8	General Comments	It is well structured. The lack of evidence limits how well it will inform the guideline. Other sources of knowledge will be needed to fill in the gaps.	Thank you for the comment..
TEP Reviewer #9	General Comments	Very well done overall and an excellent systematic review that is sorely needed in the MS field and will likely influence future research and policy dialogue and debates. It has been a pleasure to be involved in this important work.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #9	General Comments	Overall, I found the report easy to follow and logically organized. I did not find myself getting lost from one step to the next, even in areas where I am not a technical expert. The abstract and executive summary are effective and do not omit critical areas expanded upon in the full report. In reading these, I found that what I expected to find in the larger report was actually there when I read it, i.e. they prepare the reader well. The format of key points first followed by detailed discussion is very helpful.	Thank you for the comment.
TEP Reviewer #9	General Comments	I feel that the review did a great job of highlighting the weakness of the current evidence base as a whole, which is not (in my view) readily acknowledged by a large portion of the clinical community nor perhaps appreciated fully by researchers and funders at this time. The review also succeeds in identifying the high potential for bias in the current evidence base that the MS community currently clings to for guidance. This report can have a centering (and perhaps humbling effect) effect on the MS community and industry (pharma) interests that have greatly influences the research trajectory of the MS community in particular. It may also serve as a call to action for better research and better applied science in improving treatment decisions and decision quality for disease modifying treatments.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #9	General Comments	I worry, however, that it may place the MS community in the middle of a "rock and a hard place" situation, especially if policymakers and funders (who are pressured to deal with the exorbitant cost and poor cost effectiveness of MS disease modifying therapies in an accountable care environment) misinterpret the key message of the report and conclude that disease modifying treatment is largely ineffective and not worth funding. This could leave the MS community feeling stuck between the reality of current "low quality evidence" and "what do we do now while we work on getting better evidence?" What I hope this will not result in is a cessation of funding support for treatments in MS- this would be potentially catastrophic from a clinical point of view.	Thank you for the comment. We concur.
TEP Reviewer #9	General Comments	Overall, this work, in my view, and despite its potential limitations, achieves its goal. It successfully reviewed the available literature, analyzed it systematically, made its assumptions clear, and makes conclusions that will make the MS community think about our current and past assumptions and where we need to go in the future. As a MS specialist and healthcare improvement scientist makes the grade for what I was hoping to see from it. It suggests reasonable avenues for future work, will engender considerable dialogue and debate in the MS community, and suggests new avenues, such as SDM, which could potentially revolutionize the field and how we deliver MS care in the future.	Thank you for the comment.
Public Comment Section			

Commentator & Affiliation	Section	Comment	Response
APTA (cover letter in supplemental material)	Introduction	This section is clear and well-written. We have no additional suggestions.	Thank you for the comment.
CMSC IOMSN MS Section of AAN (Cover letters in supplemental materials)	Introduction	The statement in the Extended Summary that "DMTs for MS are not intended for life-long use" is a simple categorical statement, unreferenced and without supporting documentation. It should be noted that the FDA approvals of the DMTs do not specify a time-line for the duration of treatment or give recommendations regarding treatment cessation. One could question why a similar document has not been published to explore the discontinuation of an anti-platelet agent or a lipid-lowering agent in patients with known cerebrovascular disease who have not had a stroke in several years; furthermore, this question regarding treatment cessation could be extended to long-term treatment for other chronic conditions, including HIV I AIDS and cancer.	Thank you for the comment. We have revised the text regarding treatment length to “The optimal duration of DMT use remains an open and controversial question.”

Commentator & Affiliation	Section	Comment	Response
EMD Serono	Introduction	"The network analysis ranked natalizumab as the most effective drug, followed in order by IFNbeta-1a, mitozantrone, glatiramer acetate, and IFNbeta-1b. The underlined sentence must be revised to indicate the IFNbeta-1a mentioned is rebif. The draft report erroneously combines the results for Rebif and Avonex and "IFNbeta-1a" while Cochrane evaluated these products separately and found different results. In fact, the Cochrane abstract states: "From the pairwise meta-analysis, there was high quality evidence that natalizumab and IFNbeta-1a (Rebif) were effective against recurrence of relapses in RRMS during the first 24 months of treatment compared to placebo (OR 0.32, 95% CI 0.24 to 0.43; OR 0.45, 95% CI0.28 to 0.71, respectively); they were more effective than IFNbeta-1a (Avonex) (OR 0.28, 95% CI 0.22 to 0.36; OR 0.19, 95% CI 0.06 to 0.60, respectively)." The draft report accurately makes this important distinction between the interferon-1a products Rebif and Avonex on page 2 of the draft report itself. The Executive Summary must be revised accordingly.	Thank you for the suggestion. We have made the change accordingly.
EMD Serono	Introduction	"Unfortunately, the efficacy level of MS treatments appears to correlate with the frequency and severity of side effects." This statement must be revised because it is not supported by evidence. Given the variability of symptoms in a heterogeneous population, this statement is too general and is not supported by evidence when looking across the spectrum of MS DMTs. In the absence of high quality evidence (head-to-head clinical trials) ranking both efficacy and side effects, it is impossible to compare across products, particularly given the quite different side effect profiles of these treatments.	The text has been left unchanged. A reference for the sentence was provided. The sentence, and the paragraph, provides the general state of understanding that guides current clinical practice.

Commentator & Affiliation	Section	Comment	Response
EMD Serono	Introduction	"The first-line treatments, the interferon drugs and glatiramer acetate, were modestly efficacious…" This statement should be revised for clarity and accuracy. We believe that characterizing these products as "modestly efficacious" is somewhat misleading as efficacy is variable among these products and the term "modest" is relative and subjective.	Except for a minor word change, from "first-line" to "injectable", the text has been left unchanged. A reference for the sentence was provided. The sentence, and the paragraph, provides the general state of understanding that guides current clinical practice.
EMD Serono	Introduction	"Patients may switch between different DMTs in order to find one that is more effective or more tolerable, and studies have found high rates of switching between drugs." "People with MS commonly switch between the available DMTs depending on tolerance, presence of adverse effects, and perceived helpfulness of the treatment." Additional information should be added for completeness. It should be noted that patient switches also occur due to coverage changes by insurers rather than safety, efficacy, or tolerability reasons. Even stabilized patients may be forced to switch therapies due to formulary changes.	The text has been left unchanged. The purpose of the paragraph was to state the reason for the systematic review.

Commentator & Affiliation	Section	Comment	Response
EMD Serono	Introduction	"MRI to identify MS-related lesions has been shown to correlate with short-term relapse rates, 6 months to 2 years. However, long-term MRI followup as a surrogate marker for relapse rates, or, more importantly, disease progression, currently lacks evidence." This statement is no longer appropriate and should be removed. Rather than asking whether long-term MRI follow up can serve as a surrogate marker for clinical responses, the question researchers and clinicians are asking today is whether early MRS (responses) could be used as predictor of long-term clinical responses, especially disease disability status. MRI is more sensitive and tends to show response to treatment earlier than clinical responses and is expected to show higher correlation with future/long term clinical outcomes, thus it may be an appropriate predictor of future/long-term clinical outcomes. We have included as Exhibit 5 articles from Annals of Neurology, The Lancet Neurology, and Neurology that find correlation between MRI findings and relapse for your review. Further, as MRIs are more difficult, time-consuming, and expensive to perform versus clinical assessments, MRIs are not likely to be used as surrogate long-term follow up measure of clinical efficacy in the real world.	This is a different research question and is not within the scope of this review.
Novartis	Introduction	When to discontinue DMTs – review states that DMTs for MS are not intended for life-long use. Novartis response: MS is a lifelong disease with a high proportion of patients progressing to permanent disability. Currently, there is no evidence presented or cited in support of treatment discontinuation.	Thank you for the comment. We have revised the text regarding treatment length to "The optimal duration of DMT use remains an open and controversial question."

Commentator & Affiliation	Section	Comment	Response
Novartis	Introduction	"Some patients cannot tolerate any of the DMTs, but if a tolerable drug regime is determined, treatment generally continues until the individual reaches a disease course stage where DMTs no longer help. Such a point may be reached when a person is determined to be nonresponsive to the medication due to disease progression" Novartis response: Since all drugs only modify and slow disability, it is very difficult to prove that DMTs are no longer having an effect by changing the slope of the disability curve. Thus, disease progression still occurs, but this does not disprove a continuing positive effect of the drug, i.e. this does not prove DMTs are ineffective at slowing disease progression.	Thank you for the comment. Any disease that involves a general pattern of decline needs a control or comparison group to ascertain whether the slope changes over time.
Novartis	Introduction	Review states that it is too recent to include the newer drugs, including Gilenya Novartis Response: Extension studies on Gilenya (TRANSFORMS, etc), Tecfidera, Aubagio, and Tysabri should have been included here. These products are mainstay treatments with available follow-up matching the inclusion/search criteria noted in Methods section. Newer drugs are known to be more effective on ARR, MRI outcomes, etc. This review needs natural history studies on outcomes in untreated MS as a point of reference, given it stresses that more effective medications have more safety concerns. Cognition data should also be included. This review ended August 2014, so should include all available DMTs noted in the literature synthesis.	The scope of the review is for published studies longer than 3 years. All such studies meeting inclusion criteria were included. No drug was excluded by choice, only by lack of long-term studies.

Commentator & Affiliation	Section	Comment	Response
Novartis	Introduction	Pregnancy: "Neurologists commonly counsel a woman to discontinue her medications 3 months prior to trying to conceive. Unfortunately, conception isn't always easily planned and the drug holiday may continue for much longer than anticipated, possibly years." Novartis Response: It is somewhat misleading to assume that neurologists commonly counsel a woman to discontinue medications 3 months prior to trying to conceive. It would be unlikely that a neurologist would advise an MS patient with significant disease activity to discontinue medication for years. The decision to discontinue a medication prior to conception may be dependent on disease severity and the disease modifying treatment that the patient is taking at the time of a planned pregnancy (Miller D et al. Mult Scler 2014 20: 527. Gheezi A et al. Expert Rev. Clin. Immunol. 9(7), 683–692;2013.	Thank you for the comment. A sentence was added to clarify that no FDA-approved drug is labeled as Class A (safe for use in pregnancy), the sentence regarding the stopping period was removed and the paragraph revised to point out the decisions facing the MS patient and her physician.
Public Reviewer #3 David Brandes Hope MS Center	Introduction	I am a physician who specializes in the treatment of multiple sclerosis since 1972. I did the first MS fellowship in the United States from 197273 and opened the first private Multiple Sclerosis Center in the United States. I have been a Clinical Professor in Neurology at UCLA until my move to Knoxville Tennessee in 2008. I currently manage MS patients in an MS Center am involved in MS Research and speak throughout the US about MS. I have reached a point in my life where I have 21 years of experience without disease modifying therapies DMTs and 21 years with DMTs.	Thank you for your comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #4	Introduction	I believe there is an error, possibly a typo, in the classification of MS. The fourth type listed is referred to as "Primary Relapsing." The usual term for this type of MS is Progressive Relapsing. Progressive Relapsing MS is characterized by a series of distinct relapses, each with an increase in disability, without remission. This is in contrast to the straight line decline in Primary Progressive MS.	Thank you, this has been corrected.
Public Reviewer #5 Jeffrey English MS Center of Atlanta	Introduction	I do not believe that study has ever been performed that looked at decline after stopping meds in a relapsing population. This would be a harmful and foolhardy study. In phase II studies we saw increase disease activity after stopping meds	Thank you for the comment.
Public Reviewer #6 June Halper Consortium of MS Centers	Introduction	It is difficult to comprehend the rationale for this work since the MS professional community has adopted the following. Treatment with any given disease modifying medication should be continued indefinitely unless any of the following occur. Suboptimal treatment response as determined by the individual and his or her treating clinician. Intolerable side effects. Inadequate adherence to the treatment regimen. Availability of a more appropriate treatment	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #7 John Corboy U of Colorado School of Medicine	Introduction	Please see my comments below as well. There are multiple deepseated flaws with the entire context and content of this draft report. Most importantly it makes an assumption that somehow MS is a benign disease and that the meds were never meant to be used for a long time. These are unreferenced and on their face indefensible statements. The opening line says it all MS is a potentially disabling disease. Indeed it is the largest cause of disability in young American women and second largest in young American men. This concept permeates throughout the draft as many important articles are dismissed 100s of radiological studies showing its utility as a surrogate marker of MS are dismissed denies there is recurrence of disease activity when meds are discontinued and fails to mention MANY articles that clearly outline recurrence of disease activity when med are discontinued etc. Whoever wrote this either simply does not understand and know MS or has a very large axe to grind. The fact that authors and their conflicts are not listed is reprehensible. Huge chunks of the draft refer to the level of conflict for those authors referred to in the text but where is the same level of scrutiny here for the authors of this draft. This draft should go no further should not be amended should not be published. The entire premise is false.	Thank you for your comment. The review followed the AHRQ EPC methods guide in its conduct. We have revised the first paragraph of discussing the disease condition and added a sentence to the introduction "About 40 percent of people with MS receive some form of disability income" to convey the fact that this is not a benign disease for many people with MS. We have also clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. The purpose for posting the draft is for comments on the accuracy of the evidence, which should stand on its own. Therefore, the names of individuals are redacted from the draft. Authors, TEP, and KI information are provided in the published report, according to AHRQ process.
Public Reviewer #8 Lorraine Spikol Lehigh Valley Hospital	Introduction	ok	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #9 Anonymous	Introduction	Relapseremitting MS Is that like relapsingremitting MS Incomplete current DMT list. The fact there are so many common errors on the first page of the draft points to the conclusion that no one with clinical or scientific knowledge has contributed to the draft. If so God help us all.	Thank you for the suggestion. The term for progressive relapsing MS has been corrected and checked the whole report for typos and errors.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #10 Anonymous	Introduction	While the AHRQ report is well written and its summary abstract conclusions appear sane the detail document has many flaws that could lead to misinterpretation and default of discontinuing DMTs on our patients .Over the last 20 years considerable advances have been made in the delivery of multiple disease modifying treatments DMTs and their trials have provided important information for evidence based medicine approach to the treatment of MS. Unfortunately many unanswered questions remain due to the complexity of treatment and the disease itself related to best profile patient for each drug when and what appropriate switch is to be made and also one of their leading question s in their model KQ1 when should I discontinue The theoretical conceptual framework and logic path questions are accurate but unfortunately there is not one right answer that could be used as a what DMT Do I start with What should I switch to there is no step by step guide. Much less answers exist for KQ1KQ2.In this high cost of health care and DMTs all 3 questions in my opinion do require extensive review but unfortunately the heterogeneity and multifaceted aspects of multiple sclerosis have made it difficult to arrive at substantial evidence that can guide physicians step by step. Underlying reasons could be pointed to the lack of population based studies that address effectiveness of treatment. We rely heavily on the data provided from clinical trials under control situations efficacy and have little data on the effect of treatment under day to day conditions of care which relate to effectiveness. Observational studies are needed but the absence or limited availability of data suggesting a benefit or harm derived from switches or drop offs in clinical trials and the clinical experience suggesting potential of harm from discontinuation of treatment in patients suffering from MS becomes an ethical question of care. We already get denial of treatments in situations that clearly indicate switching of therapy. The report left as is would only increase denials and increase the potential of harm to our patients. I fully support that decision on discontinuation of DMTs in MS patients should be left between the patient and physician until	Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. We have also clarified in the discussion the importance of the physician's clinical experience and the patient expertise in his or her own individual experience of MS as two of the three legs of evidence-based medicine, and have highlighted the importance of shared decisionmaking. The review of the evidence highlights the state of the science and underscores important research gaps.

Commentator & Affiliation	Section	Comment	Response
#10		(cont from above) better data is provided either from randomized controls trial or observational data. We already get denial of treatments in situations that clearly indicate switching of therapy. The report left as is would only increase denials and increase the potential of harm to our patients. I fully support that decision on discontinuation of DMTs in MS patients should be left between the patient and physician until better data is provided either from randomized controls trial or observational data.	(cont from above)
Public Reviewer #16 Patient Identity withheld for privacy	Introduction	I finally received my diagnosis in Nov. of 2002, after every test available. I was given two choices by me (then) neurologist—a scooter or a wheel chair. I told him, I had a third choice—a NEW doctor!	Thank you for the comment.
APTA	Methods	In general, this section is clear and well-written. An increased level of detail to describe the critical appraisal of evidence would strengthen the review. Specifically, a detailed description of the rating criteria for study limitations, consistency, precision and bias would provide transparency in the determining of the strength of evidence.	The methods section provides a concise summary of the methods for strength of evidence. Further detail for risk of bias, which contributes to study limitation, is provided in the appendix. References to the specific methods guidance were provided for interested readers. Since meta-analysis was not possible for this evidence base, strength of evidence relied on the qualitative synthesis and was most often based on single studies.

Commentator & Affiliation	Section	Comment	Response
CMSC IOMSN MS Section of AAN	Methods	Perhaps the largest flaw of this analysis is that by arbitrarily limiting the search criteria to studies over three years in duration, all of the Class I data for the use of DMTs was eliminated, only leaving studies with a low to moderate level of evidence and a moderate to high potential for bias to support the use of DMTs in MS. All of the FDA-approved DMTs have Class I evidence for reducing relapse rates and new MRI activity, and there is substantial data that patients experiencing fewer relapses and new MRI lesions develop less disability over time. The point could be made that longer-term, placebo-controlled trials of the MS DMTs are not feasible and arguably not ethical. American Neurological Association meeting in October of 2014 suggests demonstrable benefit at 11 years in the cohort that was initially randomized to interferon beta-1b in this study. Similar data exists for other DMTs but are not included in the analysis for this guideline.	Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. This report is not a guideline. It is a systematic review of the evidence which highlights the state of the science and underscores important research gaps. No clinical recommendations are made in this report. Only published articles with sufficient information to evaluate the studies were included.

Commentator & Affiliation	Section	Comment	Response
CMSC IOMSN MS Section of AAN	Methods	The authors also discount the role of long-term MRI follow-up as a surrogate marker for relapse rates and disease progression (citing Tintore 2008); however, a meta-analysis of numerous clinical trials by Sormani et al (2009, 2013) show these correlations very clearly in the short term, and there is now voluminous data for the relationship between Tl black holes *I* brain atrophy and disease progression, much of which has been published since 2008. A large dataset by Prosperini et al (Eur J Neurol 2009) suggests that MRI stability after one year of interferon beta use predicts less disability progression at 5 years.	In fact, the long-term studies examined in this review did not use MRI as an outcome measure – it is more commonly used in clinical trials. However, Sormani meta-analysis article states "the present study does not provide direct evidence supporting the hypothesis that the early effects of a treatment on MRI markers can predict long-term effects on preventing or postponing the progression of disability." (*Sormani, M. P., Arnold, D. L. and De Stefano, N. (2014), Treatment effect on brain atrophy correlates with treatment effect on disability in multiple sclerosis. Ann Neurol., 75:43–49. doi:10.1002/ana.24018*) Moreover, the follow-up period for all included trials was 2 years, comparing MRI at 6 or 12 month with outcomes at 2 years, thus of shorter duration than studies examined in this review. MRI stability and disability progression at 5 years after one year of interferon beta would provide information on early treatments, not prolonged treatment.

Commentator & Affiliation	Section	Comment	Response
CMSC IOMSN MS Section of AAN	Methods	In addition, the methodology employed by this analysis also supports its indefensible conclusion that there are no data supporting the use of DMTs for clinically isolated syndrome (CIS). Conversely, the 5-year follow-up data of the BENEFIT trial (Kappos 2009) suggests early treatment with interferon beta- Ib for CIS delays the onset of clinically-definite and McDonald MS, and data just presented at the American Neurological Association meeting in October of 2014 suggests demonstrable benefit at 11 years in the cohort that was initially randomized to interferon beta-1b in this study. Similar data exists for other DMTs but are not included in the analysis for this guideline.	Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. This report is not a guideline. It is a systematic review of the evidence highlights the state of the science and underscores important research gaps. No clinical recommendations are made in this report.

Commentator & Affiliation	Section	Comment	Response
CMSC IOMSN MS Section of AAN	Methods	By utilizing the aforementioned methodology, this analysis does not consider existing data regarding potential harms with discontinuing DMTs. Some studies have shown that breakthrough disease occurs more commonly in patients with poor compliance to a DMT, while others have shown a return of clinical activity with cessation of interferon-beta (Richert Mult Scl 2000, Wu Acta Neurol Scan 2005, Siger J Neurol Sci 2011), natalizumab (Oconnor Neurol 2011, Fox Neurol 2014, Sorensen J Neurol 2014), and fingolimod (Ghezzi J Neurol 2013, Hakiki Mult Scl 2012). Although the authors contend that there is no disease rebound after discontinuation of natalizumab, it is clear from numerous studies, including STRATA, that patients have a return of baseline disease activity (or reoccurrence of disease activity) after stopping natalizumab, sometimes with devastating effects. Although these data may not qualify as Class I evidence, it should not be completely ignored, as the risk of accruing disability with reemergence and continued inflammatory disease is undeniably high.	Thank you for the suggestion. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. The possibility of clinical activity returning to pre-therapy levels points up the decisional dilemma faced by people with MS and their clinicians if they are contemplating discontinuing DMT therapy; return of clinical activity would confirm that the patient was not a person for whom the treatment no longer helped. If return to clinical activity after prolonged use (in the case of this review, longer than clinical trials) had been reported, such data would have been collected from the included studies. The Richert, Ghezzi, and Hakiki articles were case reports, from which it is very difficult to draw generalizations. The Siger article did not meet the followup inclusion criteria. We were unable to locate the Sorensen article mentioned. The O'Connor article was included in the Natalizumab set. We were also unable to locate the Fox article, but it might have been in reference to Kaufman J Neurol 2014 (Nov), an industry funded retrospective study of natalizumab discontinuation from patients of the RESTORE study and found that Gd+ lesion activity in patients randomized to stop receiving natalizumab was similar to control groups. The review states in the key point bullet for the KQ1 natalizumab sub-question that the evidence is insufficient to assess whether rebound exists.

Commentator & Affiliation	Section	Comment	Response
NMSS MS Coalitioni (Cover letters in supplemental material.)	Methods	The core methodology, including the framing of KQ1 and criteria for data inclusion, omits findings of importance to the doctor-patient decision-making process. Although the unidentified authors have stated clearly that the available data are insufficient to determine the long-term impact of treatment, the title, key questions and text of the report assume that discontinuation of treatment is a viable, appropriate option. By limiting their search to trials of more than three years' duration, the authors have ignored all of the Class I data demonstrating the efficacy of disease-modifying therapies (pp. 13-14). In the absence of unethical and cost-prohibitive longer-term, placebo-controlled trials, we need to rely on the best evidence available. Evidence from several studies subsequent to the pivotal trials indicates that disease-modifying therapies have an impact on the conversion from relapsing to progressive MS (pp. 10-11) and further investigations have demonstrated the impact of treatment on the evolution of persistent T1 hypointensities (known as "black holes"), which are thought to be indicative of tissue damage, and on brain atrophy (p. 14). Preventing irreversible damage is a primary goal of early and ongoing treatment.	Thank you for the comment. We have clarified in the discussion the importance of the physician's clinical experience and the patient expertise in his or her own individual experience of MS as two of the three legs of evidence-based medicine, and have highlighted the importance of shared decisionmaking. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods.
NMSS MS Coalition	Methods	In considering the role of ongoing treatment for people with MS, it is critical to look beyond the Key Questions posed in this report. In addition to looking at relapse rates, MRI activity and progression, we need to be asking how treatment over time impacts a person's ability to remain active, productive and engaged in daily life at home and at work. If we do not have sufficient data to answer those questions now, we should pursue every means to obtain the data before concluding that treatment termination is appropriate.	Thank you for the comment. We completely agree.

Commentator & Affiliation	Section	Comment	Response
Novartis	Methods	"We concentrated on outcomes relevant to the patient for decision making, such as relapse rates and changes in disability level, rather than intermediate outcomes such as lab tests for neutralizing antibodies" Novartis response: NAB occur in up to 25-30% of patients with IFN-B and may affect the outcome of long term studies. (Paolicelli D. J Neurology 2013 June 260(6).) No references have been provided to support these outcomes as those which are relevant to the patient.	Thank you for the comment. We do not believe the statement in the report to be controversial, but for clarity have amended the sentence to read "We concentrated on outcomes that patients notice or factor directly into their decisionmaking". Patient-centered outcomes have been defined by both the AHRQ EPC program and PCORI as outcomes that people notice or care about (see AHRQ Methods guide on strength of evidence as cited in the report's methods section). We focused on outcomes meeting that definition. The topic was prioritized by involving key informants who indicated that such a topic was not previously addressed and would be of value to the MS community. The key questions, and proposed outcomes, were posted for comments in June 2013.
Novartis	Methods	"This review examines the long-term (more than 3 years) consequences of discontinuing DMT. We looked for evidence that directly assessed discontinuing versus continuing DMT, and also evidence for long-term (more than 3 years) benefits and harms for either continuing or discontinuing, since the decision to continue or discontinue can be informed by the benefits or harms directly linked to either course of action." Novartis response: Natural history studies note that patients may develop symptoms such as cognitive decline 20 – 30 years later. As such, shorter studies may underestimate neurodegeneration and diffuse damage, while longer studies would pose clear challenges. MS patients may exhibit a wide variation in disease progression and underlying immunopathology. Generalized studies may not be helpful to predict differences in individual disease courses.	Thank you for the comment. We agree. This is a challenging topic to research, and much research is needed. This review provides only one step in that direction.

Commentator & Affiliation	Section	Comment	Response
Novartis	Methods	However, long-term MRI follow up as surrogate marker for relapse rates or, more importantly, disease progression, currently lacks evidence." Novartis Response: Brain Volume Loss (another long-term MRI measure) has the strongest correlation with long term disability progression, and the ability to reduce in brain volume loss with a DMT has been demonstrated in 3 Phase III clinical trials with fingolimod. However literature concerning brain volume loss was not included in this review. [Refer to oral presentation by Sormani et al from ECTRIMS 2014: Defining brain volume cut-offs to predict disability progression in MS, TRANFORMS, FREEDOMS I and II.] There is also recent data that suggests that changes in T2 lesion load may be predictive of subsequent disease progression (Sormani et al Neurology 2014). Newer imaging techniques, such as MTR and DTI, although not in general clinical use as yet, have provided even more robust correlations with long term physical and cognitive disability (Rocco et al J of Neurology:259;2012) Citations that May Contradict Quotation: Lublin et al, Neurology 2006. 61(11) : 1528-1532. Fisniku LK, et al. Brain 2008. 131 ; 808-817.	Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. The long-term studies examined in this review did not use MRI as an outcome measure – it is more commonly used in clinical trials. However, Sormani meta-analysis article states "the present study does not provide direct evidence supporting the hypothesis that the early effects of a treatment on MRI markers can predict long-term effects on preventing or postponing the progression of disability." (*Sormani, M. P., Arnold, D. L. and De Stefano, N. (2014), Treatment effect on brain atrophy correlates with treatment effect on disability in multiple sclerosis. Ann Neurol., 75:43–49. doi:10.1002/ana.24018*) Moreover, the follow-up period for all included trials was 2 years, comparing MRI at 6 or 12 month with outcomes at 2 years, thus of shorter duration than studies examined in this review.

Commentator & Affiliation	Section	Comment	Response
Novartis	Methods	"MS patients and providers have little information to guide decisions to discontinue DMT. There was no literature that directly compared continuing versus discontinuing DMT in comparable populations. There was sparse information available to address one part of the decision making picture faced by providers and patients, which is long-term benefits and harms." Novartis Response – If this is the case, given the uncertainty of disease progression, decisions to discontinue should not be made until longer term data is available. Research into this question may be challenging given ethical concerns.	Thank you for the comment. Unfortunately, people with MS today may not have the time to wait for such studies to be conducted. We have clarified in the discussion the importance of the physician's clinical experience and the patient expertise in his or her own individual experience of MS as two of the three legs of evidence-based medicine, and have highlighted the importance of shared decisionmaking.
Rocky Mountain MS Center	Methods	First, the report's analysis focuses on annual relapse reduction as the primary outcome measure in the studies. This measure is the weakest predictor of long term outcomes for MS patients. At the same time, the analysis ignored all of the secondary assessments that have been done in those same studies, including disability assessments and volumetric brain MRIs. The authors discount the role of long-term MRI follow up as a surrogate marker for relapse rates and disease progression. However, analyses of numerous clinical trials by Sormani et al (2009, 2013) show these correlations very clearly in the short term. Furthermore, there is now voluminous data for the relationship between brain atrophy and disease progression in studies published since 2008.	Annual relapse rate is one of the most commonly reported outcomes. The long-term studies examined in this review did not use MRI as an outcome measure – it is more commonly used in clinical trials. However, Sormani meta-analysis article states "the present study does not provide direct evidence supporting the hypothesis that the early effects of a treatment on MRI markers can predict long-term effects on preventing or postponing the progression of disability." (*Sormani, M. P., Arnold, D. L. and De Stefano, N. (2014), Treatment effect on brain atrophy correlates with treatment effect on disability in multiple sclerosis. Ann Neurol., 75:43–49. doi:10.1002/ana.24018*) Moreover, the follow-up period for all included trials was 2 years, comparing MRI at 6 or 12 month with outcomes at 2 years, thus of shorter duration than studies examined in this review.

Commentator & Affiliation	Section	Comment	Response
Rocky Mountain MS Center	Methods	Second, the observation that the studies were only 2 years in length and couldn't confirm that there was long-term benefit is a pejorative way to ask the question. It would be more appropriate to ask is there any evidence that they lose efficacy over time and there is no evidence that that occurs. By limiting the scope of study search criteria, the AHRQ draft report completely ignores the concept of preserving brain volume in order to maximize lifelong brain health in patients as a therapeutic goal using modern therapies. There is very strong evidence (Sormani, et al) demonstrating that if you combine brain volume changes with new lesion activity you can explain between 70 and 80% of the variance in terms of outcomes related to increasing disability. Therefore, the appropriate discussion should be about identifying best practices in the use of disease modifying therapies in order to maximize health outcomes from the patient perspective.	Thank you for the comment. Had the question been asked as suggested here, the current evidence base would still have been relevant, and the findings the same. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. The question of what are the effects of early treatment is not the same as the question what are the effects of prolonged treatment. In fact, the long-term studies examined in this review did not use MRI as an outcome measure – it is more commonly used in clinical trials. However, Sormani meta-analysis article states "the present study does not provide direct evidence supporting the hypothesis that the early effects of a treatment on MRI markers can predict long-term effects on preventing or postponing the progression of disability." (*Sormani, M. P., Arnold, D. L. and De Stefano, N. (2014), Treatment effect on brain atrophy correlates with treatment effect on disability in multiple sclerosis. Ann Neurol., 75:43–49. doi:10.1002/ana.24018*) Moreover, the follow-up period for all included trials was 2 years, comparing MRI at 6 or 12 month with outcomes at 2 years, thus of shorter duration than studies examined in this review.

Commentator & Affiliation	Section	Comment	Response
Rocky Mountain MS Center	Methods	Finally, the paper ignores the natural history of MS which has been documented in multiple studies specifically the fact that the inflammatory phase of the disease is most intense at the onset of the disease and gradually diminishes over time. So a discussion of withdrawal of therapy should be focused on identifying patients that have moved through the active inflammatory phase and appear to be in a state of remission from the standpoint of inflammatory disease. This is not likely to occur in patients under the age of 55, but does seem to increase substantially in prevalence as patients reach the age of mid-60's and beyond.	We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. By design, our analysis looks at people who may be in the remission phase and not acute onset because they had to have had prolonged used.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #3 David Brandes	Methods	My clinical experience with thousands of MS patients over this time is that patients have done much better over the years with DMTs than without DMTs. Most MS patients no longer require wheelchairs or walkers since the era of DMTs. I have many patients who have discontinued therapy for various reasons: lack of funding, insurance, injection fatigue, side effect fatigue, etc. and over time disease activity and relapse begin again. Sometimes the disease activity begins 5 or more years after discontinuation....and often these relapse leave behind permanent neurological deficits. Many of our studies over the past 10 years show that the average patient on placebo has relapses every 2.53 years so about 50 of patients wont have recurrent relapse until 3 or more years have passed. Therefore in reviewing the quoted literature there is not enough time without treatment to determine that treatment should be discontinued in individual patients. Treating the average patient with MS is not adequate. With regards to patients with progressive disease I have been treating them for many years. In my personal experience using combination therapies either interferon or glatiramir plus low dose methotrexate or other immunosuppressant plus monthly IV methylprednisolone about 80 of my secondary progressive patients and 60 of my primary progressive patients have stopped progressing. I cannot assess if the other patients progress more slowly than would have been expected since I do not have a prolonged placebo controlled trial.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
#3		(cont) However based on my personal experience with many hundreds of progressive patients it would be essentially a criminal act to discontinue their treatments. There is some evidence that MS tends to burn out in more advanced age groups. At one point in time about 10-20 years ago it was thought that MS stopped progressing in people in their 50s or 60s. However more recent data looking at atrophy progression shows that it is about the same in MS patients in their 70s and 80s. This would suggest that MS may burn out at these ages and this may be the time to discontinue medication. However in my practical experience I newly diagnosed a patient with MS at the age of 72 and have kept her on disease modifying therapy over the past 2 years. The decision about discontinuation of DMTs will not be easy in this case.	
Public Reviewer #6 June Halper Consortium of MS Centers	Methods	Methods used by the unnamed experts are shady at best. They eliminate all trials under two years most of which have resulted in FDA approval for relapsing forms of MS.	The purpose for posting the draft is for comments on the accuracy of the evidence, which should stand on its own. Therefore, the names of individuals are redacted from the draft. Authors, TEP, and KI information will be provided in the published report, according to AHRQ process. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. The Methods section provides details of the methods used in the report. The evidence report utilizes methods developed by AHRQ EPC program in collaboration with several experts. They are consistent with other established methods such as those by Cochrane and IOM

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #8 Lorraine Spikol Lehigh Valley Hospital	Methods	Limiting review to peer reviewed literature in a field with such paucity of data to answer the question is inappropriate. Data from employment hospitalization etc might help determine if there are outcomes that are useful but were overlooked in your review	Thank you for the suggestion. Systematic review methodology is dependent on data from previously conducted studies. Primary data collection and analysis is outside the scope. We limit our data to published literature for purposes of rigor – the ability to assess the reliability and generalizability of the studies is fundamental to systematic review methodology.
Public Reviewer #9 Anonymous	Methods	Invalid. Cherrypicking literature to support your beliefs is wrong.	Thank you for the comment. The literature search and screening methods followed AHRQ EPC guidance. The evidence report utilizes methods developed by AHRQ EPC program in collaboration with several experts. They are consistent with other established methods such as those by Cochrane and IOM
Public Reviewer #16 Patient identity withheld for privacy	Methods	After meeting Dr. [redacted for privacy] two weeks later, I started using Rebif injections. The side effects, mostly bruising for the needles proved difficult, but I used Rebif three times per week or 6 years. I have been a clinical trial subject since 2009, using Lemtrada (Alemtuzimab), an infusible medication. During these past five years, I have only had one major exacerbation. Other than minor issues, I have not experienced much in the way of noticeable progression of MS symptoms.	Thank you for the comment.
APTA	Results	We have no specific comments to this section.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
CMSC IOMSN MS Section of AAN	Results	The analysis on potential harms with the DMTs does not consider the significant risk of developing physical and emotional disability from MS, which the DMTs are designed to limit. Every medication has the potential for side effects, some of which may be intolerable, and certainly the DMTs are no exception. Many drugs also come with potentially serious risks, including the risk of PML with natalizumab pointed out in the AHRQ document. The authors inappropriately conflate tolerance and risk, which are obviously very different things, and then they incorrectly relate DMT tolerance and efficacy without offering data to support that relationship. They then discuss potential harms from long-term DMT use (although the risks are not appreciably increased in the long-term except for the obvious exception of natalizumab in the JC virus positive patient) but completely ignore the risk of harm from MS itself, which the DMTs attempt to limit. Multiple sclerosis is not as benign disease as the authors imply; indeed, it is the most common cause of non-traumatic neurologic disability in young adults in the US. After 8 years of disease, many patients have ambulatory dysfunction; at 15 years, over 50% of patients require an assistive device to walk, and at 25 years, many patients are in a wheelchair. The disability from MS has an impact on hundreds of thousands of individuals (including the patient and their family / social network) as well as the economic community and the nation as a whole. In reality, the risk of a DMT needs to be balanced against the risk of burdensome and widespread disability from MS.	Thank you for the comment. We have revised the first paragraph discussion the disease condition in the introduction and added a sentence to the introduction “About 40 percent of people with MS receive some form of disability income” to convey the fact that this is not benign.”

Commentator & Affiliation	Section	Comment	Response
CMSC IOMSN MS Section of AAN	Results	This analysis pays much attention to the British Columbia cohort (Shirani et al, JAMA, 2012); however, there are multiple issues with this study that only includes one class of DMT (interferons). It compares the outcomes for a historical MS cohort (diagnosed by Poser criteria) with a contemporary (diagnosed by either Poser or McDonald criteria) interferon-treated and a contemporary untreated cohort. Although the table suggests some differences in the groups, it is notable that the contemporary treated (n=868) and the contemporary untreated (n=829) were nearly identical in size; presumably, there was some factor that drove the choice between treatment and non- treatment in the individual patients that may represent a selection (indication to treat) bias. There were also a significant number (436) of patients excluded from the contemporary cohorts because of lack of adequate disability data, and there are notable differences in the cohorts. The study did not distinguish which interferon was used (EVIDENCE and INCOMIN studies suggest potential superiority of high-dose, high-frequency interferon), or the potential presence of interferon neutralizing antibodies (NAbs). Interestingly, a similarly large study by Trojano et el (2007) regarding the natural history of MS treated with interferon reached the opposite conclusion (interferon delayed progression to SPMS) but is not cited by the authors of this guideline.	Thank you for the comment. The evidence based on the Shirani 2012 articles was rated as low-strength, acknowledging the study limitations and the possibility that future research may change the findings.

Commentator & Affiliation	Section	Comment	Response
CMSC IOMSN MS Section of AAN	Results	The discussion on patient and MS physician preferences (Key Question 2) does not have enough data for inclusion in a guideline. We suspect that the variability in the intrapersonal and interpersonal preferences present in a physician-patient relationship is even greater than the heterogeneity in MS and should never be relegated to an algorithmic guideline.	Thank you for the comment. We have clarified in the discussion the importance of the physician's clinical experience and the patient expertise in his or her own individual experience of MS as two of the three legs of evidence-based medicine. This report is not a guideline. It is a systematic review of the evidence which highlights the state of the science and underscores important research gaps. No clinical recommendations are made in this report.
EMD Serono	Results	"Low-strength evidence from one moderate risk of bias study suggests that interferon use did not change disability progression for RRMS patients." These statements are inaccurate, we suspect likely due, in part, to not distinguishing between the different interferon products. Further, it is inaccurate for Rebif. According to its FDA-approved label, Rebif is indicated "for treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disabiality." Please refer to section 14 of the Rebif prescribing information (Exhibit 1). Further, we have provided the article "Randomised double-blind placebo-controlled sutyd of interferon beta-1a in relapsing/remitting multiple sclerosis" (The Lancet, Vol. 352, Nov 7, 1998) as Exhibit 2 and call your attention in particular to Tables 2 and 3 and Figure 2 on page 1501. As the study supporting the disability claim in the Rebif label was a randomized, double-blind, placebo controlled clinical trials, the above statements should be revised to convey that high-strength evidence shows that Rebif (interveron beta-1a) use delays physical disability progression.	As the article upon which the key point lies does not identify specific interferon therapies, we cannot speak beyond what was provided. We clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods.

Commentator & Affiliation	Section	Comment	Response
EMD Serono	Results	"One high risk of bias study used selected patients' data from a Swedish MS registry, also using both a contemporary and historical cohort as comparisons. Adjusting for sex, age at MS symptom onset, whether onset was monofocal or polyfocal, and location of lesions, the study did not find a statistically significant difference in time to SPMS conversion for DMT (interferons and glatiramer acetate) treated versus a historical control of untreated patients." This section should be revised as it misrepresents the paper's primary conclusion. We encourage the agency to take a second look at this study, keeping in mind the significance of "time period" versus "treatment initiation time." Upon review, we believe you will find that there was a significant difference in "time period," meaning statistically significant differences between the contemporary treated group and the historical group, which indicated that the treated group had significantly longer time to SPMS versus the historical control group (hazard ratios: men, 0.32; women 0.53). It is important to note that no head-to-head, randomized, well controlled trials have been conducted to specifically assess the "time to SPMS" measure. To distinguish, the insignificant "treatment initiation time" indicated that the duration of treatments did not reach statistical significance.	Thank you for the suggestion. While graded as insufficient evidence with which to draw a conclusion, this study, along with the other high risk of bias study, was presented in more detail because it represented an attempt to address the question of interest directly. Research of this nature is challenging and the report acknowledges their efforts, while at the same time point out the study deficiencies that led to the high risk of bias assessment. We agree that the text did not properly characterize the study and have amended the text.
EMD Serono	Results	In addition, we are concerned by the value the Agency assigned to the Shirani A, Zhao Y, Karim MD, et al. We would like to draw your attention to a letter to the editor of the Journal of the American Medical Association which points out some concerns with the article which it seems the Agency overlooked. The letter is provided as Exhibit 3.	Thank you for the comment. The evidence was rated as low-strength, acknowledging the study limitations and the possibility that future research may change the findings.

Commentator & Affiliation	Section	Comment	Response
NMSS MS Coalition	Results	Evidence is accumulating that disease-modifying treatment needs to be ongoing. The FDA indications for the disease-modifying therapies are not time-limited; each is approved for use in those with relapsing forms of MS, whether a person's disease is relapsing for only a few years or for a lifetime. In the absence of controlled clinical trials to assess the impact of treatment discontinuation, we must rely on the accumulating evidence suggesting that treatment needs to be ongoing for benefits to persist, and that cessation of treatment negatively impacts clinical and MRI outcomes. [See NMSS report.] Given these findings, it seems inappropriate to frame the key question around determining the effectiveness of discontinuing treatment. People with MS would be better served by further study of the benefits of treatment continuation and the risks of treatment termination.	Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. The topic was prioritized by involving key informants who indicated that such a topic was not previously addressed and would be of value to the MS community. The key questions were posted for comments in June 2013.

Commentator & Affiliation	Section	Comment	Response
Novartis	Results	"No studies directly assessed the consequences of continuing versus discontinuing DMT in comparable populations. Low strength evidence from one moderate risk of bias study suggests long-term all-cause survival is higher for treatment naïve relapse-remitting MS (RRMS) patients who did not delay starting interferon beta 1b by 2 years and used DMTs for a longer duration than those who started later. Low strength evidence from one moderate risk of bias study suggests that interferon use did not change disability progression for RRMS patients. Insufficient evidence was available for long-term benefits for DMT for secondary progressive MS (SPMS) patients, and most outcomes for RRMS patients. Except for those noted above, studies were at high risk of bias, had small sample sizes, and had reported effects small in magnitude." Novartis Response: Evidence cited in this review is all low strength, and only comes from 2 studies on interferons. One of the studies range from 4.5 to 10 years; A more recent study from the same author as above using data from the study cited in the AHRQ (Shirani et al European Journal of Neurology 2014, 21: 835–844) states "RRMS patients with more frequent relapses at baseline may be more likely to benefit from interferon beta treatment with respect to long-term disability progression." Also, there are no data on cognitive outcomes. With the lack of evidence for discontinuing DMTs, would a design of such a study be ethical?	The Shirani 2014 follow-up to the Shirani 2012 study examined 5 potential subgroups, one of which was the patient's average relapse rate. The subgroup difference was found for the historical control group but not the concurrent control group, and only for EDSS 6, not EDSS 4. The study used a Bonferonni correction for 5 subgroup types, but did not adjust for the multiple control groups and EDSS levels. The results may be intriguing, but do not yet rise to the level of low strength of evidence. Lack of evidence alone cannot be the determiner for ethical research. While such research is challenging, it is not impossible. It may be hard to recruit subjects for an RCT, but even observational studies could be done. Designing studies that account for the inevitable case-mix problems would require skill.

Commentator & Affiliation	Section	Comment	Response
Novartis	Results	Discontinuations due to Short and Long term Safety: "Limited low strength evidence suggests harms over the long term (up to 16 years for interferon, 22 years for glatiramer acetate, and 8.5 years for teriflunomide) do not differ from short-term harms. The majority of discontinuation tends to occur in the short-term (2 to 3 years from start). Broad variation in harms reporting precludes informative aggregation and summary. Evidence is insufficient for whether rebound after discontinuing natalizumab exists due to the high risk of bias and small study sample sizes." Novartis Response: The FDA has acknowledged (www.fda.gov) that the use of a drug to treat a disease should be put into context of the ratio of the drug's benefit to its risk. Since MS is not a benign disease (Scalfari etal. Brain 2010: 133; 1914–1929) and the clinical course can vary significantly between patients, reporting short and long term safety should be put into the context that certain MS patients may require medications that confer both short and long term safety issues. There are also newer strategies to mitigate short and long term safety issues, such as the use of JC antibody testing for natalizumab (Tur C, Montalban X. CNS Drugs. 2014 Jul;28(7):641-8), first dose observation with fingolimod (Gilenya label) and longer blood monitoring with other medications (Tecfidera label, Aubagio label). In addition, short term and long term data collected by a number of manufacturers has been monitored closely and reported periodically. In the case of Gilenya, Novartis has reported safety data over a 10 year period with a cumulative total of 137,500 patient years and over 100,000 patients treated within trials and in the post-marketing setting. As of February 2014, there has been no change in the long term safety as compared to the short term safety (Camm Jet al. Am Heart J 2014;0:1-13., Francis G et al Multiple Sclerosis Aug 15, 2013, PSUR 7, 2014).	Thank you for the comment. To help clarify, we have specified that in this case short-term means the 2-3 year period covered by clinical trials.

Commentator & Affiliation	Section	Comment	Response
Novartis	Results	Side effects discontinuation: "The included studies used a wide range of reporting methods and adverse event categories that precluded simple aggregation over the studies. The most commonly reported adverse events were injection site reactions, flu-like symptoms, depression, and headache. Serious adverse events were generally not reported, although two studies gave rates of about 25 percent to 30 percent of participants. Discontinuations tended to occur during the first or second year of the study. When reported, discontinuation rates during long-term followup were low, about 3 percent to 4 percent, but rates due to adverse events were not separate from total discontinuation rates, which would also include perceived lack of efficacy and other reasons not necessarily related to adverse events or side effects. Further, all studies lost participants to attrition" Novartis Response: Due to the older studies included in the review, side effects noted are typical of injectable DMTs, and do not represent the current marketplace of available oral therapies. If reported discontinuation rates during long-term followup were low (3-4%), and were comprised of various discontinuation types (due to adverse events, perceived lack of efficacy and other reasons not necessarily related to adverse events or side effects), rates of each discontinuation type were evidently low. Further, as noted previously, 10 year data on Gilenya made available as of Feb 2014, reflecting 137,500 patient years and over 100,000 patients treated within trials and in the post-marketing setting, indicates no change in the long term safety as compared to the short term safety (Camm Jet al. Am Heart J 2014, Francis G et al Multiple Sclerosis Aug 15, 2013, PSUR 7, 2014). This applies to serious as well as non-serious adverse events categories (SAEs and AEs). All studies are subject to attrition, particularly in the longer-term (study period or follow-up).	Thank you for the suggestion. The key bullet point for KQ1b has been amended to state: 'Limited low strength evidence suggests harms for injectable DMTs over the long term (up to 16 years for interferon, 22 years for glatiramer acetate, and 8.5 years for teriflunomide) do not differ from short-term harms."

Commentator & Affiliation	Section	Comment	Response
Novartis	Results	Patient and provider preferences. [KQ2] Novartis Response: We agree these points are preliminary, given currently available data has been excluded. Discontinuation, preferences, and treatment patterns from the physician and patient perspectives have been shown to be complex based on the literature to-date, and do not simplify as indicated above. In terms of the studies included, 3 studies reference data from The Netherlands (2 were published a decade or more ago). Information regarding the patient's MS condition, treating physician type, available therapies, and practice patterns are not elaborated. Without this information, and considering the vast geographical, health care and chronological divide, generalizability may be quite limited. In terms of 'paradoxical preference', the above study findings may not reflect DMT efficacy but the patient's situation as a newly diagnosed individual with a lifelong, lesser known, complex, chronic disease. It may be intuitive that during this period of acclimation, DMT use may be perceived as less preferential or accepted, whereas later on disease progression, with a better understanding of the clinical course of the disease, a more solid foundation of knowledge would be present to inform knowledgeable decision-making. Regarding decision making, data from NARCOMS registry (Salter 2013) regarding switching further contradicts the notion that patients drive decisions. This study demonstrated the origin of the discussion to switch was split equally between the responder initiating the conversation and the physician suggesting the idea. Doctor's recommendation (24.9%) was the most frequently reported reason to switch medications prior to lack of efficacy (13.6%). Without additional data, the decision to discontinue approved DMTs is a risky and unfounded one. MS Centers known for excellence such as the Cleveland Clinic independently offered the following guidance, in support of early and continuous therapy: "It is likely the accumulation of irreversible tissue damage limits the potential for benefit from DMT as the disease progresses. The therapeutic nihilism of the past should be replaced by aggressive treatment and monitoring, while carefully balancing the potential risks and benefits." [http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/neurology/multiple_sclerosis/]	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #3 David Brandes Hope MS Center	Results	The use of evidence based medicine is very important to help control costs and prevent irrational use of testing and treatments but experienced physicians know that the lack of evidence based studies does not mean that treatment is ineffective.A specific example is the approval of Ampyra dalfampridine to improve gaitwalking speed in MS patients. In the study patients were divided into responders and nonresponders. When the data was analyzed many more patients on medication were responders compared to those on placebo. However if the comparison was done between all patients on placebo and all patients on drug the results were not statistically significant. This was due to the fact that only about 3543 of patients were responders. In some cases we have found in other conditions that only 1020 percent of patients are responders. If evidence based medicine looks only at the average responsiveness the medication would seem to be ineffective and would not be approved.	Thank you for the comment. We have clarified in the discussion the importance of the physician's clinical experience and the patient expertise in his or her own individual experience of MS as two of the three legs of evidence-based medicine, and have highlighted the importance of shared decisionmaking.
Public Reviewer #4	Results	Virtually all studies show that early intervention with DMT results in less disability later in the course of the disease. The FDA classifies DMT as ongoing (with the exception of mitoxantrone). Patients who stay on treatment tend to show less effects of the MS in the long term.	Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods.
Public Reviewer #4	Results	There is repeated reference to a decisive lack of studies and the low reliability factors of the cited studies. Much work remains to be done before making the assumption that DMT is less effective than is currently believed by the medical professionals treating the patients.	Thank you for the comment. The Discussion section summarizes the results and notes that much work is needed to provide an evidence-base to inform and support clinician experience and patient preferences.
Public Reviewer #6 June Halper Consortium of MS Centers	Results	The results and conclusions of this work is that there are no conclusions since the evidence is weak and the paper is even weaker.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #8 Lorraine Spikol Lehigh Valley Hospital	Results	Since how to define when disease modifying rx is ineffective is so difficult it made results questionable. It seems there is no agreement on how to tell if a patient will benefit or not.	Thank you for the comment.
Public Reviewer #9 Anonymous	Results	Must understand how to interpret scientific literature and published studies in order to draw conclusions. This is obviously not the case.	Thank you for the comment. The evidence report utilizes methods developed by AHRQ EPC program in collaboration with several experts. They are consistent with other established methods such as those by Cochrane and IOM
Public Reviewer #16 Patient identity withheld for privacy	Results	I am experiencing many productive, happy years, with almost no exacerbations, especially since beginning the Lemtrada. At only 58 years of age, I believe if it were not for my MS DMT; I would not be mobile & as independent as I am now! I'd probably be living with physical and emotional issues which would reduce my quality of life.	Thank you for the comment.
APTA	Discussion	We have no specific comments to this section.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
CMSC IOMSN MS Section of AAN	Discussion	One of the issues with the MS DMT literature is a paucity of quality comparator trials; unfortunately, there are even fewer treatment cessation trials. One of the reasons for this is the lack of a funding source, as the pharmaceutical industry has little to gain from funding these trials. A potentially more appropriate path for EHC AHRQ to take would be funding a study that would attempt to answer the question of DMT discontinuation; however, eliminating bias in this study will be difficult (as it will essentially be rater-blinded), and designing the trial to appropriately answer the question (length of time, end-points, drop-out) will be challenging. Given the previous travesties of the Tuskegee study, there are obvious ethical issues of withholding treatment, so obtaining IRB approval and recruiting subjects for this study may be challenging. Despite this, we would still recommend consideration of such a study, because the issue of treatment discontinuation is a question that needs an answer for both patients and medical economics.	Thank you for the comment. We have added to the future research needs section "Since the pharmaceutical industry would not benefit from strong comparator studies focusing on treatment discontinuation, other funding sources will need to be identified."

Commentator & Affiliation	Section	Comment	Response
EMD Serono	Discussion	"Quality of life benefits of treatment are offset by quality of life decreases due to side effects and risk profiles are important." This statement must be removed or revised as there is no evidence to support it as written. As written, this statement draws the conclusion that quality of life (QOL) benefits are offset by side effects. We are not aware of any evidence supporting this statement. The impact of treatment to QOL, and impact of side effects on QOL, are both highly individualized to each patient. Treatment decisions are in the hands of physicians and patients, who are best suited to determine whether the side effects and risk profile of any particular treatment "offset" its efficacy which may impact quality of life. Given the lack of evidence on this topic, we believe this statement – if it were to remain in the final report – could be harmful to patients and it therefore must be removed.	The sentence has been edited slightly from its original form, but the meaning remains essentially unchanged. In making treatment decisions, it is always important for the patient and physician to consider both benefits and side effects. A net benefit to quality of life is not a controversial position.

Commentator & Affiliation	Section	Comment	Response
EMD Serono	Discussion	"Newly approved drugs, such as fingolimod, and drugs in the development pipeline are emphasizing oral administration to improve medication uptake and adherence to treatment programs." This statement must be removed because it is misleading. This statement erroneously implies that fingolimod, and other orally administered MS DMTs, improve treatment adherence. FDA has not recognized any effect on adherence for any of these products as evidenced by no associated claim in the products' labels. To date, there is no conclusive data supporting the premise that oral administration leads to greater uptake or adherence for MS patients. Evidence suggests many factors influence adherence. A 2003 report by the World Health Organization (WHO), Adherence to Long-Term Therapies: Evidence for Action, examined adherence for nine chronic conditions and risk factors. The WHO found that adherence is influenced by several factors including "the social and economic factors, the health care team/system, the characteristics of the disease, disease therapies and patient-related factors." It concluded that "solving the problems related to each of these factors is necessary if patients' adherence to therapies is to be improved." Although the report does not examine adherence to MS therapies specifically, we believe its findings are generalizable to the broader community of patients with chronic disease. The report is available at: http://www.who.int/chp/knowledge/publications/adherence_report/en/	The sentence has been amended to "are emphasizing oral administration, which may improve medication uptake and adherence to treatment programs."

Commentator & Affiliation	Section	Comment	Response
EMD Serono	Discussion	"The initial 2-year results published in 2009 found patient outcomes were worse than predicted:" This section is incomplete and misleading and must be revised. It appears that key information was excluded from this section. A 2014 BMJ Open article by Palace J, Bregenzer T, TremlettH, et al., "UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model," concluded that the control dataset and analysis model upon which the initial 2-year results were based were false. We strongly suggest that the Agency review this article, provided as Exhibit 4, and revise accordingly. We suggest the following revision is necessary in order to accurately convey the current posture of the 2-year results: "The initial 2-year results published in 2009 found patient outcomes were worse than predicted; however, an independent group who reviewed the data concluded that both the control dataset and analysis model selected when setting up the risk-sharing scheme, had intrinsic flaws."	We have added the sentence: "However, results were controversial; an independent group who reviewed the data concluded that both the control dataset and analysis model selected when setting up the risk-sharing scheme, had intrinsic flaws."

Commentator & Affiliation	Section	Comment	Response
NMSS MS Coalition	Discussion	The absence of data should not be confused with the presence of negative data; further study is needed determine if and when treatment should be terminated. The report states clearly that more data are needed to determine the long-term impact – both positive and negative – of treatment with disease-modifying therapies. However, the very existence of this report makes it likely that third parties will use the absence of positive data as a justification for terminating treatment. Given the variability of the disease from one individual to another, and the unpredictability of the disease course for any individual, shared decision-making by any person with MS and his or her healthcare professional must rely on all the available evidence that might shed light on appropriate options. While none of the studies may be perfect, the growing body of evidence, as cited in the MS Coalition consensus paper, strongly points to the importance of early and ongoing treatment with a disease-modifying therapy.	Thank you for the comment. We have clarified in the discussion the importance of the physician's clinical experience and the patient expertise in his or her own individual experience of MS as two of the three legs of evidence-based medicine, and have highlighted the importance of shared decisionmaking.
NMSS MS Coalition	Discussion	We are fortunate to have several medications with different mechanisms of action from which a patient and doctor can choose. Terminating treatment prematurely will deprive people with MS and their doctors from finding that optimal treatment. Therefore, the emphasis should be on gaining a greater understanding of the reasons why people with MS may opt to terminate treatment and addressing them individually within the doctor-patient relationship.	We have clarified in the discussion the importance of the physician's clinical experience and the patient expertise in his or her own individual experience of MS as two of the three legs of evidence-based medicine. We also added to the future research section the suggestion to "explore why and under what circumstances a patient might seek to terminate treatment."

Commentator & Affiliation	Section	Comment	Response
NMSS MS Coalition	Discussion	At this point in time, two of the most recent papers examining numerous studies on the continuation/discontinuation of disease modifying treatment in MS are the MS Coalition consensus document and this draft report. While taking different approaches, both papers suggest that there is a lack of clear indicators as to when treatment should be discontinued. The AHRQ draft report states on page ES-2, "the determination of when DMT is no longer helpful is challenging". The draft report further states that additional research is needed in these areas. The [NMSS] consensus paper states that treatment with any given disease-modifying medication should be continued indefinitely unless any of the following occur: • Sub-optimal treatment response as determined by the individual and his or her treating clinician • Intolerable side effects • Inadequate adherence to the treatment regimen • Availability of a more appropriate treatment The above sections in these comments refer to evidence documenting that early and ongoing treatment is the best current option for people with MS to delay progression of the disease and preserve physical and cognitive function and independence. Without evidence to support the appropriate time to discontinue treatment, the National MS Society supports the approach in the consensus paper which provides better access to disease modifying medications for people with MS. Since it is well known that third-party payers develop guidelines based on AHRQ reports, we strongly urge AHRQ to either decline to finalize the report or include stronger language to prevent denials of access to treatment for people who might benefit. We suggest specific language stating that there is insufficient evidence to indicate the appropriate time to discontinue treatment and therefore the report should not be used as guidelines in this area.	Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. We have also clarified in the discussion the importance of the physician's clinical experience and the patient expertise in his or her own individual experience of MS as two of the three legs of evidence-based medicine.

Commentator & Affiliation	Section	Comment	Response
Novartis	Discussion	Thus when considering the low strength evidence interferon studies, the heterogeneity of the disease, changing treatment paradigms, a lack of data on the effect on cognition and the evolution of newer and more efficacious DMTs , it would be extremely difficult to determine when to discontinue a DMT.	Thank you for the comment.
Novartis	Discussion	Self-injection can be a deterrent to patients with MS starting first-line DMTs and "shot-fatigue" is a significant factor for adherence. Oral medications will certainly have implications for preferences for continuing and discontinuing DMTs" Novartis Response: Forgetting injections and other injection-related reasons (i.e., tired of taking injections, pain at injection site, injection anxiety, skin reactions, do not feel need for every injection, no one available to administer) are common reasons for non-adherence to injectable DMTs in new as well as existing patients (Raimundo 2012, Devonshire 2011, Treadaway 2009). Oral medications have certainly changed patient preferences. Data provided by patients previously taking IFNs/GA switching to fingolimod indicated mode of administration was the most cited reason for therapy change (Cascione, 2013). Several other studies confirm oral mode of administration as the strongest patient preference (e.g. Wilson 2012). As further illustration, willingness to consider switching back to injectable therapy was lowest in patients taking fingolimod (Salter 2012). Given the review's exclusion of oral agents and related data, we feel this synthesis is limited. Modern day options of DMTs and therefore the current understanding of patient preferences and factors related to discontinuation cannot adequately be addressed as such.	Thank you for the comment. The implications of the oral medications are noted in the discussion section on pg 50. Oral medications were not excluded from the review. They did not appear in the results section because of the lack of published studies with greater than 3 years of followup.

Commentator & Affiliation	Section	Comment	Response
Novartis	Discussion	"Second, similar to determining which CIS patients will convert to MS, or which MS patients have a benign disease course without use of DMTs, the transition from relapse-remitting MS (RRMS) to SPMS is difficult to ascertain and therefore poses challenges in the decision to discontinue treatment. There are no clear biomarkers and no distinct boundaries for the transition. Further, how does one differentiate between a "stable" RRMS, one which may be induced by DMTs preventing relapses, and SPMS? Currently, EDSS changes or a score of 6 or 7 and clinical judgment are generally used. However, patients who may be "close" to SPMS but "stable" may look similar, and without clear clinical markers to differentiate, both provider and patient are left with uncertainty" Novartis Response: We totally agree that there are multiple uncertainties and challenges in determining progression in MS. Recent papers have suggested that patients diagnosed with "benign MS" do go on to have cognitive and physical disability with time, suggesting that this disease is less benign than previously thought (Bester M et al J Neurol Sci. 2013 Jul 15;330(1-2):61-6). As to clinical approach to SPMS, based on the new classification as outlined in Lublin et al (Lublin F. et al. Neurology 2014;83:1–9), progressive disease includes several subgroups not previously recognized in past studies. Thus it would be very difficult to assess not only the effect of DMTs on conversion to SPMS but also the effect of DMTs on SPMS in a retrospective analysis of the data. In view of our better understanding of the underlying pathophysiology of MS one might question whether we have any credible data on when to discontinue DMTs	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Novartis	Discussion	The diagnosis and treatment of Multiple Sclerosis are solely between the patient and the physician. Guidelines are just that, guidelines, and should never be construed to be a rule or used for intervention by third parties.	Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. We have also clarified in the discussion the importance of the physician's clinical experience and the patient expertise in his or her own individual experience of MS as two of the three legs of evidence-based medicine. This report is not a guideline. It is a systematic review of the evidence which highlights the state of the science and underscores important research gaps. No clinical recommendations are made in this report.
Public Reviewer #3 David Brandes Hope MS Center	Discussion	Based on many years of experience as well as many discussions with MS physicians throughout the United States and the rest of the world it seems that discontinuation of therapy could be dangerous in many MS patients. This decision should be left to the expert treating physician and the patient associated with careful followup of new disease activity clinically or by MRI. It should not be forced by rigid protocols which would likely be adopted by payers simply to reduce the overall cost of care. No one really thinks that antihypertensive medication should be discontinued if the patient hasnt had a stroke or heart attack in a certain period of time. Why should we stop MS DMTs. In my opinion based on years of treatment and research in the field of MS protocols for discontinuation of therapy are not adequate. In particular this proposed publication is inaccurate misleading and nearly a criminal act. At this point in time the decision on discontinuation of DMTs in MS patients should be left to the expert treating physician and the patient. Thank you for publically presenting this proposal and allowing reasonable and scientific discussion.	Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. The report informs provides the state of the science to help inform decisions to continue or discontinue treatment. We have also clarified in the discussion the importance of the physician's clinical experience and the patient expertise in his or her own individual experience of MS as two of the three legs of evidence-based medicine. This report is not a guideline. It is a systematic review of the evidence which highlights the state of the science and underscores important research gaps. No clinical recommendations are made in this report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #6 June Halper Consortium of MS Centers	Discussion	Although there is still much that we do not fully understand about the pathophysiology of MS the last 20 years have provided a significant number of treatment options that improve prognosis and quality of life for people with MS. Furthermore the growing body of evidence highlights the importance of early and ongoing access to diseasemodifying therapies. I do not understand why money was spent on this futile and poorly designed exercise that can do nothing but harm the professional and patient community in MS.	The topic was prioritized by involving key informants who indicated that such a topic was not previously addressed and would be of value to the MS community. The key questions were posted for comments in June 2013.
Public Reviewer #8 Lorraine Spikol Lehigh Valley Hospital	Discussion	Until specific reproducible criterion to determine which patients have ongoing active disease and which have slow progression I do not think we can state with certainty who will and will not benefit from treatment. The studies cited are too short to assess benefit in a life long disease. The outcome measures are too removed from clinical relevance EDSS to be helpful in determining who would not benefit.	Thank you for the comment.
Public Reviewer #16 Patient identity withheld for privacy	Discussion	If DMTs are discontinued as the approved treatment for Multiple Sclerosis, I believe we'll go back to the days of the over use of steroids, which not only have severe side effects of their own, but a strong cause of osteopenia and osteoporosis, with only temporary relief of exacerbation. DMT's provide protection from these occurring.	Thank you for the comment.
APTA	References Abbreviations and Acronyms	We have no specific comments to this section	Thank you for the comment.
Public Reviewer #9 Anonymous	References	The idea this draft is proposing has absolutely no supporting evidence.	Thank you for the comment.
APTA	Tables Figures Appendixes	This section is clear and well-written. We have no additional suggestions.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #9 Anonymous	Appendixes	Please provide the list of authorsstudents of this draft. I would like to see if anyone above an 8th grade reading level contributed to this draft.	The purpose for posting the draft is for comments on the accuracy of the evidence, which should stand on its own. Therefore, the names of individuals are redacted from the draft. Authors, TEP, and KI information will be provided in the published report, according to AHRQ process.
APTA	General Comments	Multiple Sclerosis is a complex and highly variable disease. The decision to start, continue or discontinue a disease modifying therapy is also a complex one. Numerous clinical trials have demonstrated varying degrees of efficacy, safety and tolerability for currently available treatment options. Given the complexity of MS treatment and the lack of any guiding data, the decision to discontinue a disease modifying therapy is best made between the person with MS and their healthcare team. We would like to emphasize that the healthcare team should be an interprofessional collaborative that includes the patient.	We have clarified in the introduction and discussion the importance of the physician's clinical experience and the patient expertise in his or her own individual experience of MS as two of the three legs of evidence-based medicine.
APTA	General Comments	It is important to clearly state that there is no conclusive evidence that supports whether or not a treatment should be discontinued. For instance the statements on page 16, KQ1 Key points – the last bullet states "Insufficient evidence was available for long-term benefits for DMTs…" can be misleading. As this report identifies, there is little evidence in any regard with relation to Disease-Modifying Treatments (DMT) for MS. This statement could be misconstrued by payers to mean they should not pay for DMT for either Primary relapsing MS or Relapse remitting MS.	We amended the last key point bullet for KQ2 on page 17 to: "Insufficient evidence was available to assess long-term benefits"

Commentator & Affiliation	Section	Comment	Response
APTA	General Comments	We believe that this draft comparative effectiveness review of "Discontinuation of Disease-Modifying Treatment for Multiple Sclerosis" is very important and the identification of issues regarding this area is key. By increasing the awareness of the limitations of the evidence, there will be an improved understanding of research needs that will lead to improve decision making and improved quality of life for the individuals with MS.	Thank you for the comment.
CMSC IOMSN MS Section of AAN	General Comments	The Effective Health Care (EHC) Program Agency for Healthcare Research and Quality (AHRQ) recently created a draft guideline for the discontinuation of the disease-modifying treatment (DMT) for multiple sclerosis (MS). Surprisingly, based on the potential impact of this work, the identity of the "experts" who contributed to this document is not disclosed in the draft. The audience for this document is defined as "healthplans, providers, purchasers, government programs, and the health care system as a whole," a rather presumptuous outreach that does not include patients with MS or those who care for them. Although the authors appropriately say that there are limited data to guide decisions about discontinuing DMTs, our grave concern is that this document will be used by health-care payers to limit access to DMTs for patient with MS as an absence of evidence is often construed as evidence for a lack of an effect. This document was distributed to the members of the MS Section of the American Academy of Neurology (AAN) for comment. We, as a group of MS experts, have cited numerous and serious flaws and concerns with the document	Thank you for the comment. The purpose for posting the draft is for comments on the accuracy of the evidence, which should stand on its own. Therefore, the names of individuals are redacted from the draft. Authors, TEP, and KI information will be provided in the published report, according to AHRQ process. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. We have also clarified in the discussion the importance of the physician's clinical experience and the patient expertise in his or her own individual experience of MS as two of the three legs of evidence-based medicine. This report is not a guideline. It is a systematic review of the evidence which highlights the state of the science and underscores important research gaps. No clinical recommendations are made in this report.

Commentator & Affiliation	Section	Comment	Response
CMSC IOMSN MS Section of AAN	General Comments	As guidelines are apt to do, this document fails to appreciate the heterogeneity of the disease in question, in this case MS. Multiple sclerosis is an inflammatory condition of the central nervous system that occurs when a genetically susceptible individual is exposed to an environmental trigger. Most agree that there are at least two substrates involved with the pathophysiology of the disease, including inflammation and degeneration. Although potentially confounded by selection bias, Luchinetti et al have described four different pathologic subtypes of the disease. The International Multiple Sclerosis Genetic Consortium (IMSGC) has identified almost 150 genetic loci that can increase the risk of the disease, and many agree that MS may be mediated by either Thlor Thl 7-mediated immune processes. Furthermore, there have been four different diagnostic criteria for MS (Poser; McDonald 2001, McDonald 2005, McDonald 2010) since the approval of the first MS DMT (Betaseron) in 1993. Classically, MS has been subtyped into RR (relapsing remitting), SP (secondary progressive), PP (primary progressive), and PR (progressive relapsing). However, these subtypes were designed more to homogenize clinical trial populations than to describe different pathophysiologic subtypes of the disease. These subtypes were recently revised to include clinically isolated syndrome (CIS), RR-MS with active and progressive modifiers, and PP-MS with active and progressive modifiers. Although many still try to categorize MS into specific ordinal categories, it is obvious that MS is a very heterogeneous disease spanning a continuum of pathophysiology ranging from almost entirely) inflammatory to almost entirely degenerative with numerous potential clinical outcomes ranging from benign to malignant. This significant heterogeneity and the lack of biomarkers to stratify and individual's MS explains the relatively unpredictable course of the disease and complicates the assessment of the efficacy of incompletely effective DMTs in the individual patient, but this heterogeneity does not negate the copious amount of data supporting the use of DMTs in patients with MS as early as possible after diagnosis with a substantial effort to sustain adherence.	Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. We have also clarified in the discussion the importance of the physician's clinical experience and the patient expertise in his or her own individual experience of MS as two of the three legs of evidence-based medicine. This report is not a guideline. It is a systematic review of the evidence which highlights the state of the science and underscores important research gaps. No clinical recommendations are made in this report. Minor revisions to the MS type descriptions have been made and the Lublin 2014 article cited. However, since the included literature was based on the previous typing scheme, we believe it is most helpful to readers to remain with the basic scheme.

Commentator & Affiliation	Section	Comment	Response
CMSC IOMSN MS Section of AAN	General Comments	Evidence-based medicine (EBM) is a powerful tool that has greatly improved the quality and cost-effectiveness of medical care, but like any quality tool, it can be misused. A common question that occurs is what to do when there is no evidence; however, EBM does not suggest that nothing should be done in this case and does not devalue a physician's gestalt and the physician-patient relationship. EBM and personalized medicine are not mutually exclusive; consider Sackett et al BMJ 1996: "The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research ... External clinical evidence can inform, but can never replace, individual clinical expertise, and it is this expertise that decides whether the external evidence applies to the individual patient at all..." The use of DMTs in MS is justified by EBM, given their wealth of supporting adequate and well-designed clinical trials. On the contrary, similar evidence does not exist for DMT cessation, so the rationale for this proposed guideline puzzles our community of healthcare experts.	Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. We have also clarified in the discussion the importance of the physician's clinical experience and the patient expertise in his or her own individual experience of MS as two of the three legs of evidence-based medicine. This report is not a guideline. It is a systematic review of the evidence which highlights the state of the science and underscores important research gaps. No clinical recommendations are made in this report.

Commentator & Affiliation	Section	Comment	Response
CMSC IOMSN MS Section of AAN	General Comments	Although there has been much publicity about disclosing physicians' conflicts of interest, one should realize that all scholastic organizations also have conflicts of interest. The lack of transparency about the authors, their affiliations, and the motivation behind this proposed guideline is troublesome; indeed, the error of identifying PRMS as "primary relapsing multiple sclerosis" in this document raises significant questions about their expertise with MS. The EHC was created under the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, and the AHRQ is under the umbrella of the US Department of Health and Human Services. AHRQ has a Congressional appropriation to conduct research driven by the needs of Medicare, Medicaid, and the State Children's Health Insurance program. This is also true for the American Academy of Neurology (AAN) given its interactions with Congress and the insurance industry as well as the financial support that it receives from the pharmaceutical industry. Conflicts of interest are not necessarily bad, but it is essential that they be adequately disclosed. The impetus and rationale for this guideline is unclear given our knowledge of multiple sclerosis, its inexorable course prior to the advent of disease modifying therapy, and the breadth of current research supporting early and sustained treatment of MS. One might construe an economic motivation, as the burgeoning cost of healthcare has been one of the predominant issues discussed in politics in recent years. Few MS neurologists will disagree that the exponential increase in the price of MS DMTs is highly unrealistic and unsustainable. A recent analysis by Dr. Jacqueline Palace presented at ACTRIMS/ECTRIMS 2014 suggested that if DMT prices were lower, the long-term use of DMT would be cost-effective.	The purpose for posting the draft is for comments on the accuracy of the evidence, which should stand on its own. Therefore, the names of individuals are redacted from the draft. Authors, TEP, and KI information will be provided in the published report, according to AHRQ process. Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. This report is not a guideline. It is a systematic review of the evidence which highlights the state of the science and underscores important research gaps. No clinical recommendations are made in this report.

Commentator & Affiliation	Section	Comment	Response
EMD Serono	General Comments	We do not believe evidence supports the draft report's overall presumption that disease modifying treatment (DMT) should be discontinued. We are not aware of any evidence, and do not believe there is any evidence in the draft report, that supports the draft report's presumption that discontinuation of treatment is recommended. Although we fully acknowledged that there is not evidence supporting a presumption that life-long treatment is beneficial (the safety and efficacy of treatment with Rebif beyond 2 years have not been established), lack of evidence for life-long treatment is not a sufficient basis from which to draw a conclusion that discontinuation is necessary. We encourage the Agency to keep in mind that its findings could be used by payers to limit access to therapy. It is therefore imperative that presumptions and conclusion with such implications, such as this one – be supported by evidence or removed prior to finalizing this report.	Thank you for the comment. We have revised the text regarding treatment length to "The optimal duration of DMT use remains an open and controversial question." We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. This report is not a guideline. It is a systematic review of the evidence which highlights the state of the science and underscores important research gaps. No clinical recommendations are made in this report.

Commentator & Affiliation	Section	Comment	Response
EMD Serono	General Comments	Interferon beta-1a therapies and Interferon beta-1b therapies should be differentiated throughout the report; the Interferon beta-1a therapies must also be differentiated from each other when appropriate. The five interferon therapies currently approved in the US are different products with different efficacy and safety profiles. For example, two of the interferon beta-1a products are indicated for patients with relapsing forms of MS to "decrease the frequency of clinical exacerbations" and to "slow" (Avonex) or "delay" (Rebif) "the accumulation of physical disability." In contrast, the two interferon beta-1b products are not shown to be effective against the accumulation of physical disability in their FDA-approved labels. Further, among the interferon beta-1a products, patients treated with Rebif 44 mcg three times per week were more likely to remain relapse-free at 24 an 48 weeks than were patients treated with Avonex 30 mcg once per week in a head-to-head clinical trial. We have provided as Exhibit 1 the Rebif Prescribing Information (PI) and encourage the Agency to thoroughly review the PIs for all products in the interferon class and revise the report accordingly prior to finalizing.	Thank you for the comment. It would not be possible to separate the Interferon beta therapies throughout the report as many studies themselves did not differentiate the therapies.
CMSC IOMSN MS Section of AAN	General Comments	In summary, and based on the above, this proposed AHRQ guideline has no evidence to support it as a guideline. On the contrary, if distributed to healthcare payers, it may cause untold damage to multiple sclerosis care and return us to an era when multiple sclerosis was a "diagnose-adios" disease for which neurologists were advised that the best way to ruin a medical career was to take on the treatment of MS. A potentially more appropriate path for EHC AHRQ is to fund a well-designed study that would seek to answer the question of the impact and outcomes of DMT discontinuation.	Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. This report is NOT a guideline. It is a systematic review of the evidence which highlights the state of the science and underscores important research gaps. No clinical recommendations are made in this report.

Commentator & Affiliation	Section	Comment	Response
NMSS MS Coalition	General Comments	We believe there are several core problems within the draft report and methodology used. Given that third parties within the healthcare system will likely use this report to inform treatment guidelines and insurance coverage decisions, it is critical that everyone within the MS community has confidence in the methodology and report, and that the report not prohibit healthcare providers and people with MS from making the right treatment decisions for each individual. Given the evidence that treatment should be ongoing and the lack of evidence as to when to discontinue disease modifying treatment, we urge that the report not be finalized at this time. If it is finalized, we suggest specific language stating that there is insufficient evidence to indicate the appropriate time to discontinue treatment and therefore the report should not be used as guidelines in this area.	Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. This report is NOT a guideline. It is a systematic review of the evidence which highlights the state of the science and underscores important research gaps. No clinical recommendations are made in this report.
NMSS MS Coalition	General Comments	The impact of this disease on individuals and families is not addressed. The report overly focused on risks and harms from staying on treatment, with little attention to the risks of the disease itself. Multiple sclerosis is a variable and unpredictable disease that affects each individual differently.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Novartis	General Comments	Novartis would like to thank the AHRQ authors for the opportunity to comment on this document and appreciate the comprehensive nature of the review. Based on the comments provided above, we suggest this response be reopened and the methodology expanded to include additional key content. In order to adequately explore the questions at hand, the scope of this synthesis should address the following: natural history studies; oral DMTs; related data on cognition, PROs, patient treatment preferences; and qualitative evaluation of provider prescribing insights. Based on what is known and unknown to date, Novartis recommends that, due to the paucity of data regarding discontinuation of DMTs or because of disease severity, firm conclusions about when to discontinue DMTs should be avoided. We do agree that additional long term data is needed to better understand the important issues raised in this analysis.	Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. This report is not a guideline. It is a systematic review of the evidence which highlights the state of the science and underscores important research gaps. No clinical recommendations are made in this report.
Rocky Mountain MS Center	General Comments	In our opinion, the draft report is seriously flawed. Instead of moving forward with this report and potentially jeopardizing the care of MS patients, we strongly recommend that the EHC AHRQ instead focus efforts on ensuring the best possible combination of DMTs and other treatments to maximize lifelong brain health in MS patients and promote the highest quality of care. We believe the draft report is flawed for the following reasons: [see above]	Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. This report is not a guideline. It is a systematic review of the evidence which highlights the state of the science and underscores important research gaps. No clinical recommendations are made in this report.

Commentator & Affiliation	Section	Comment	Response
Rocky Mountain MS Center	General Comments	Unfortunately, based on these serious flaws, the draft report has no evidence to support it as a guideline for discontinuation of DMTs. We are very concerned that the report will impact MS patients negatively and lead MS treatment down a destructive path of non-treatment. Instead, the AHRQ should focus efforts on ensuring the best possible combination of DMTs and other treatments to maximize lifelong brain health in MS patients and promote the highest quality of care.	Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. This report is not a guideline. It is a systematic review of the evidence which highlights the state of the science and underscores important research gaps. No clinical recommendations are made in this report.
Public Reviewer #1 Derek Smith MS Care of CT	General Comments		

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1 Derek Smith MS Care of CT	General Comments	In 2010, NICE after >decade of resisting paying for MS medications, concluded that they are cost-effective, and approved their use. Thousands of UK MS patients became irreversibly neurologically disabled while NICE performed their 'scientifically grounded' evaluation. (http://www.dh.gov.uk/dr_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4012214.pdf) The first report on the scheme was published in late 2009, with details of patients' outcomes for 2005-7. Disease progression was not only worse than predicted by the model used by NICE, it was worse than that in the untreated control group. This dramatic finding did not, however, trigger any price reduction. Instead, the paper reports: "The scientific advisory group considered that it was premature at this stage to reach any decision about re-pricing the drugs without further follow-up and analyses." Various reasons were given, including possible underestimation in the model, that use of historical controls may miss changes in the disease, and the effects of a "no improvement" assumption. Each of these arguments has been strongly contested by McCabe and colleagues, most of whom took part in the original modeling. (McCabe C, Stafinski T, Edlin R, Menon D, Banff AED summit. Access with evidence development schemes.	Thank you for the comment. The risk sharing scheme is included in the discussion section as an example of a research approach. We did not evaluate the study from a policy or reimbursement perspective.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1 Derek Smith MS Care of CT	General Comments	A framework for description and evaluation. Pharmacoeconomics 2010;28:143-52). By 2014, using newer methodologies and control groups, it was concluded that the MS injectable DMTs are cost-effective. (Palace et al. UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model. BMJ Open. 2014 Jan 17;4(1):e004073. doi: 10.1136/bmjopen-2013-004073). For the NHS, however, the scheme can be judged only "a costly failure" as suggested by the House of Commons Health Committee which raised concerns about the Scheme for several years. The biggest losers are the other NHS patients who would otherwise have benefited from the money spent on the scheme .(Shirani A, Zhao Y, Karim ME, et al. Association between use of interferon beta and progression of disability in patients with relapsing-remitting multiple sclerosis. Jama 2012; Jul 18;308(3):247-56. PMID: 22797642., see also QUASMS in this regard)	Thank you for the comment. The risk sharing scheme is included in the discussion section as an example of a research approach. We did not evaluate the study from a policy or reimbursement perspective.
Public Reviewer #1 Derek Smith MS Care of CT	General Comments	Actual MS specialists (who have years of training and experience) and not Policy specialists are in the best position to make decisions about treatment or non-treatment of this unpredictable, heterogenous illness. The first questions before any such policy statements are commissioned should be 1. Might this harm patients and 2. Might the funds for this be better used to treat patients? At the very least, the abysmal NICE experience suggests that practicing MS clinicians (who almost all have impressive clinical trial experience) should be included in any discussion about 1. what are the important policy questions and 2. how to answer them.	Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. This report is not a guideline. It is a systematic review of the evidence which highlights the state of the science and underscores important research gaps. No clinical recommendations are made in this report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2	General Comments	My comments will be brief as the comments that have already been submitted by the MS Coalition are supported in full by this writer. The assumptions made by the unnamed authors of the Draft Document regarding Discontinuation of Disease-Modifying Treatment for Multiple Sclerosis are weak when there is little genomic data to support their intention to discontinue therapies. The ability to identify individual patient responders and non-responders has not yet been substantiated. Future studies, designed to gather the genomic data to personalize therapy to specific agents, are needed. Racial, as well as ethnic, differences in response to treatments are noted by clinicians dealing with the actual patients. It is premature to say there is "evidence-based" data to stop therapy in this complex neurological disease.	Thank you for the comment. The purpose for posting the draft is for comments on the accuracy of the evidence, which should stand on its own. Therefore, the names of individuals are redacted from the draft. Authors, TEP, and KI information will be provided in the published report, according to AHRQ process. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. We have also clarified in the discussion the importance of the physician's clinical experience and the patient expertise in his or her own individual experience of MS as two of the three legs of evidence-based medicine. This report is not a guideline. It is a systematic review of the evidence which highlights the state of the science and underscores important research gaps. No clinical recommendations are made in this report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #3 David Brandes Hope MS Center	General Comments	This should not be published. Is this a continuation of the attempt to prevent treatment of progressive MS patients? Who is recommending this article? If it is published, there should be room in the journal for many disagreements, both at the time it is published and afterwards. I have been involved in research and the treatment of MS patients since 1972. I spent 21 years without any approved disease modifying therapy (DMT) for MS patients, and we are now "celebrating" the availability of DMT's for 20 years. So despite the advent of DMT's, over half of my professional life in MS has been spent without DMT's. Below are my reasons for recommending that such an article not be published. The methods described are simply opinions. The reasons for potentially stopping MS Disease-Modifying Therapy include lack of benefit, side-effect management and cost of treatment. The reasons for continuing treatment include recognized benefits, unrecognized benefits and fear of worsening disease without treatment. The reasons for stopping are obvious and really need not be discussed. How about the reasons for continuing? They aren't so obvious, since a lack of relapses, lack of progression, lack of new lesions on the MRI scan and even just slowing of progression are not so obvious. If the disease is stable, or if the progression is slowed, how is it possible to tell if the disease has "burned out" or if the medication is preventing neurological deterioration? We have no specific way to measure if disease modifying therapy is actually working. We can stop the medication and then watch what happens. However, re-activation of the disease is likely to cause permanent neurological deficits. This is not simply a flaring up of joint pain,	Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. This report is not a guideline. It is a systematic review of the evidence which highlights the state of the science and underscores important research gaps. No clinical recommendations are made in this report.

Commentator & Affiliation	Section	Comment	Response
#3		(cont from above) We have no specific way to measure if disease modifying therapy is actually working. We can stop the medication and then watch what happens. However, re-activation of the disease is likely to cause permanent neurological deficits. This is not simply a flaring up of joint pain, diarrhea/cramping or new skin lesions. It's damage to the brain, spinal cord and/or optic nerve, which are currently not reversible. Some have said that there is evidence that the disease "burns out" in later life. Some have postulated in the 50-60 age group, some in the 70's and 80's. I recently newly diagnosed a patient with MS at the age of 74, when she had her 3rd relapse (the first two were not recognized). Clinical history, examination, MRI and CSF were both very consistent with MS, and no other cause was identified. This patient did not have "burn out" of her disease, even at the age of 74. As noted above, I have cared for MS patients since 1972. The age of DMT's has made a great difference in the outcome of MS patients based on personal observation among most long-term MS specialists. A recent article from Canada noted no difference in outcomes for patients taking interferons vs those not receiving treatment. However, a study in 2011 demonstrated that adherence to MS DMT's in Ontario, Canada was very low at about 60%.	(continued from above)

Commentator & Affiliation	Section	Comment	Response
#3		(cont from above) I have treated Secondary progressive MS patients with a combination of interferon, monthly IV Solu-Medrol and methotrexate since the late 1990's. In my personal experience, about 80% of these patients have stopped progressing for 5 years or more. Although the other 20% have progressed, they may be progressing more slowly. Since this is not a placebo controlled trial, I can't tell if the disease has slowed down. Interestingly, with the same treatment, about 2/3 of my primary progressive patients have also stopped progressing for 5 years or longer. How can we deny treatment for progressive MS patients? How can we elect to stop treatment at all? The ethics of stopping or not treating are frightening. I recommend against developing guidelines to stop treatment, as the insurance companies will use this to great advantage to prevent treatment of many appropriate MS patients.	(continued from above)
Public Reviewer #4	General Comments	Thank you for the opportunity to comment as part of the peer review of this document. I am both a person living with Multiple Sclerosis and a retired doctor. - I do not serve as my own health care provider; I have taken 50% of the maximum lifetime dose of mitoxantrone and have not taken any other DMT.	Thank you for the comment.
Public Reviewer #4	General Comments	The report fails to consider the devastating effects on the family. Often MS is a disease of young mothers. Every member of the family is affected in a myriad of ways.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #5 Jeffrey English MS Center of Atlanta	General Comments	The conclusion is very unclear and alarming. MS is a slow disease but very disabling to many most of whom are women. Designing a study to show stopping meds have no effect on outcome is impossible.	While it is challenging, it is not impossible. It may be hard to recruit subjects for an RCT, but even observational studies could be done. Designing studies that account for the inevitable case-mix problems would require skill.
Public Reviewer #6 June Halper Consortium of MS Centers	General Comments	Under the Freedom of Information Act please inform your readers who wrote this poorly written paper which may do much more harm than good.	The purpose for posting the draft is for comments on the accuracy of the evidence, which should stand on its own. Therefore, the names of individuals are redacted from the draft. Authors, TEP, and KI information will be provided in the published report, according to AHRQ process.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #8 Lorraine Spikol Lehigh Valley Hospital	General Comments	I have practiced in the community setting since 1991. Given the limitations of our knowledge I have always told my patients treatment holds out their best hope for prevention of disability. Given that we have no options for repair of the CNS prevention is our patients best hope. I have not had excessive difficulty motivating pts to stay on rx nor have I seen severe side effects or safety issues. At many Academy of Neurology meetings I have asked on my pts behalf Who can come off rx and never got an answer that could be applied in a rigorous way. In a disease without good biomarkers affecting a young population over many many years during which the activity of the disease can randomly cause a lot or a little permanent CNS damage I think we should continue to encourage research and treatment. Our MS Center participates in research and would be happy to participate in any endeavor to help solve this. However I would strongly urge the AHRQ not to jeopardize access to rx with recommendations based on incomplete data. Withdrawal of rx must be based on good scientific data my patients and my colleagues are looking forward to this I do not think this document represents this data.	Thank you for the comment. This report is not a guideline. It is a systematic review of the evidence which highlights the state of the science and underscores important research gaps. No clinical recommendations are made in this report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #9 Anonymous	General Comments	See Parachute use to prevent death and major trauma related to gravitational challenge systematic review of randomised controlled trials by Gordon Smith in the BMJ. Summary as follows Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.Design Systematic review of randomised controlled trials.Data sources Medline Web of Science Embase and the Cochrane Library databases appropriate internet sites and citation lists.Study selection Studies showing the effects of using a parachute during free fall.Main outcome measure Death or major trauma defined as an injury severity score 15.Results We were unable to identify any randomised controlled trials of parachute intervention.Conclusions As with many interventions intended to prevent ill health the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind randomised placebo controlled crossover trial of the parachute.	Thank you for the comment. We have clarified in the discussion the importance of the physician's clinical experience and the patient expertise in his or her own individual experience of MS as two of the three legs of evidence-based medicine.
Public Reviewer #11 Alan Segaloff Multiple Sclerosis Foundation	General Comments	We support David E. Jones MD Chair MS Section of AAN and the Medical Partnership 4 MS response Multiple Sclerosis Foundation	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #12 Jonathan Hosey, American Academy of Neurology Practice Committee	General Comments	Thank you for the development of this draft systematic review. It is the intention that the Guideline Development Dissemination and Implementation Subcommittee of the American Academy of Neurology will use this and other existing published systematic reviews to develop a clinical practice guideline. I am writing to ask that you consider these comments are part of the review. 1. It is important to realize that regardless of the title or the methodology of the report the paper may be used to deny payment by third party payers. Consider adding a statement on page 17 as the last line of the statement of the key points to remind the reader that absence of evidence is not absence of effectiveness.	Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods. We also amended the last key point bullet no page 17 to: "Insufficient evidence was available to assess long-term benefits"
Public Reviewer #12 Jonathan Hosey, American Academy of Neurology Practice Committee	General Comments	2. The authors also discount the role of long term MRI followup as a surrogate marker for relapse rates and disease progression citing Tintore 2008 however a metaanalysis of numerous clinical trials by Sormani et al 2009 2013 show these correlations very clearly in the short term and there is now voluminous data for the relationship between T1 black holes brain atrophy and disease progression much of which has been published since 2008.	In fact, long-term studies examined did not use MRI as an outcome measure – it is more commonly used in clinical trials. However, Sormani meta-analysis article states "the present study does not provide direct evidence supporting the hypothesis that the early effects of a treatment on MRI markers can predict long-term effects on preventing or postponing the progression of disability." (*Sormani, M. P., Arnold, D. L. and De Stefano, N. (2014), Treatment effect on brain atrophy correlates with treatment effect on disability in multiple sclerosis. Ann Neurol., 75:43–49. doi:10.1002/ana.24018*) Moreover, the follow-up period for all included trials was 2 years, comparing MRI at 6 or 12 month with outcomes at 2 years, thus of shorter duration than studies examined in this review.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #12 Jonathan Hosey, American Academy of Neurology Practice Committee	General Comments	3. Consider removing this statement on page 32 that DMTs for MS are not intended for lifelong use. This is a simple categorical statement which is unreferenced and without supporting documentation. Either find a reference or delete	We have revised the language regarding the intended period of use of DMTs so that the report, and readers, remain focused on the continuing decisional dilemma of when discontinuing treatment is appropriate for MS patients with prolonged DMT treatment plans.
Public Reviewer #12 Jonathan Hosey, American Academy of Neurology Practice Committee	General Comments	4. Consider creating a section to inform the reader of the potential harms with discontinuing DMTs. There may be safety data to consider incorporating and referencing including side effects that can be painful to patients.	We reported in the results section for KQ1b what is available in the published literature for long-term benefits or harms for continuing or discontinuing treatment for people with MS who have used DMTs for prolonged (longer than 3 years) periods.
Public Reviewer #13 Nancy Sicotte CedarsSinai Medical Center	General Comments	The authors and their relevant disclosures must be provided. There is clearly not enough evidence available yet to definitively determine the appropriate timing or risks of discontinuing disease modifying treatments in MS patients. The collection of these data should be the focus of efforts moving forward.	The purpose for posting the draft is for comments on the accuracy of the evidence, which should stand on its own. Therefore, the names of individuals are redacted from the draft. Authors, TEP, and KI information will be provided in the published report, according to AHRQ process.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #14 Robert McBurney Accelerated Cure Project for Multiple Sclerosis	General Comments	General Comments on the Draft Comparative Effectiveness Review entitled Discontinuation of Disease Modifying Treatment for Multiple Sclerosis from Accelerated Cure Project for Multiple Sclerosis ACP Robert McBurney PhD Chief Executive Officer Hollie Schmidt MS VP Scientific Operations and Leadership of the Steering Committee for the OPTUP Clinical Study Revere Kinkel MD Chair University of California San Diego Benjamin Greenberg MD MHS Vice Chair University of Texas Southwestern When we examine the AHRQ Draft CE Review and also have read some of the excellent comments sent on behalf of patients and practitioners we agree that there is simply insufficient robust evidence upon which to base a definitive decision about this aspect of MS treatment. Moreover the community of MS patients and clinicians lack robust evidence to make the choice of which DMT is most appropriate for which patient. These and other crucial needs in MS treatment formed the basis for the development of the OPTUP Optimizing Treatment Understanding Progression Clinical Study that has been thoughtfully created over the past 2 years through a close collaboration amongst ACP and clinicians at 9 of the original 10 MS clinics that participated in successful ACPs Repository program and with input from many other individual and commercial stakeholders including a Community Advisory Panel of people with MS and caregivers. With initial sponsorship already received to cover all startup activities OPTUP is on a path to first patient enrolled in April of 2015. An outline of the OPTUP Clinical Study has been uploaded to provide additional information in support of these comments.	Thank you for the comment. This review does indeed support efforts to improve our knowledge base to support physicians and patients in medical decision making. The project has been noted in the Future Research section as an example of current efforts.

Commentator & Affiliation	Section	Comment	Response
#14		(cont from above) We believe that OPTUP is the clinical study that is poised to generate the robust evidence that is called for both in the Draft Review and in some of the comments that we have read. In the OPTUP study MS patients who discontinue treatment with DMTs remain in the study and continue to be evaluated by all outcome measures. OPTUP is beyond shovel ready and is on a path to launching enrollment in the very near future. There might still be an opportunity to tweak the protocol design without interfering with the timeline. We have commitments from 9 initial clinical sites we are in discussions with additional individual clinical sites and MS clinical networks the Steering Committee and group of initial external advisors are in place all vendors CRO EDC system and Biorepository have been selected we have an imminent vendor kickoff meeting and we are within a month or so of IRB submissions. Therefore in addition to the excellent letters sent on behalf of patients and practitioners which make written comments about the Draft Review it is possible to point to an action that is taking place to address this key topic through a comprehensive clinical study that will generate robust evidence on this topic and many others of importance to optimizing the treatment of MS and to understanding the basis of progressive disability. It seems to us that it would make sense to table the draft document while supporting the OPTUP Clinical Study and other studies that will generate the much needed results to support evidence based medicine in multiple sclerosis.	(cont from above)

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #15 Chris LaGanke North Central Neurology Associates	General Comments	As can be concluded from the analysis no credible conclusion regarding benefit to continuing or discontinuing DMT can be made. Therefore as was alluded to in the introduction no guideline can substitute for individual clinical judgment. No evidence exists to alter the individual judgment then which should be left unregulated. This concept was the concept from the original doctrine of evidence based medicine by Sackett et al where the conclusion is that both the best available evidence and the clinicians expertise should be used to render treatment decisions. In the absence of good available evidence we are left with the clinicians judgment. I think there is little doubt that the individuals we placed on DMTs 15 years ago are far more ambulatory than the individuals we did not place on DMT 30 years ago and assessed 15 years ago. Definitely not quantified and considered scientific evidence but undoubtedly true and most important	Thank you for the comment. We have clarified in the discussion the importance of the physician's clinical experience and the patient expertise in his or her own individual experience of MS as two of the three legs of evidence-based medicine. This report is not a guideline. It is a systematic review of the evidence which highlights the state of the science and underscores important research gaps. No clinical recommendations are made in this report.
Public Reviewer #16 Patient identity withheld for privacy	General Comments	Consider, please the millions of patients world wide living with an unpredictable disease. I'm certain there is enough scientific evidence to show DMTs work for most all of us!	Thank you for the comment. We have clarified in the introduction that the efficacy of DMTs has been recently reported elsewhere and the goal of this report was to address those patients who have used DMT for prolonged periods.