Evidence-based Practice Center Systematic Review Protocol

Project Title: Discontinuation of Disease-Modifying Treatment for Multiple Sclerosis

I. Background and Objectives for the Systematic Review

Multiple sclerosis (MS) is characterized by destruction of the myelin sheath (the insulating layer around the nerves in the brain and spinal cord) and axon loss within the central nervous system. MS affects 2.5 million individuals worldwide and approximately 400,000 in the United States. MS affects twice as many women as men and diagnosis usually occurs between the ages of 20 and 50.[1] Symptoms and disease course both can be heterogeneous and highly individualized, depending on where the lesions occur within the central nervous system and the type of MS. People with clinically isolated syndrome (CIS), a first neurological episode that lasts at least 24 hours and is caused by inflammation or demyelination in one (monofocal) or more (multifocal) sites in the central nervous system, may or may not go on to develop MS. MS types include:

- Relapse-remitting MS (RRMS) is the most common form of MS, affecting approximately 85 percent of patients. Patients typically are diagnosed in their 20s or 30s. Symptoms often present over a course of days, stabilize, and spontaneously resolve; however, over time permanent disability often develops and progresses with further relapses. Over 25 years, 90 percent of patients with RRMS will transition to secondary progressive MS.[2]
- Secondary progressive MS (SPMS) is characterized by worsening disability with or without relapses. Patients may have exacerbations, but the trend over time is a relatively steady progression of disease and disability.[1]
- Primary progressive MS (PPMS) affects about 15 percent of patients and women and men about equally. This form has the worst prognosis and is characterized by gradual and progressive worsening.[1]
- Primary relapsing MS (PRMS) affects about 5 percent of patients. This form is usually initially diagnosed as PPMS and changed to PRMS when the patient experiences a relapse.

The underlying etiology of MS is the subject of ongoing debate within the research community. Most existing literature addresses MS as an autoimmune, inflammatory disease that, in turn, is the basis for current drug treatments.[3] Others, however, suggest that MS is at base a neurodegenerative disease for which the autoimmune response is the body's reaction to the neurodegenerative debris.[4] Still others hypothesize that MS is a chronic metabolic disorder.[5] However, the autoimmune activity—whether it is eventually shown to be a primary or secondary cause—has led to the treatment options available today.

The main challenge facing clinicians and patients is choosing a course of treatment. MS cannot be cured with current therapies.[6] Attention, therefore, turns to treatment options to slow the disease progression and relieve symptoms to improve quality of life. Unfortunately, the efficacy level of MS treatments appears to correlate with the frequency and severity of side effects.[7] For those patients with RRMS who have converted to SPMS, current disease-modifying treatments are limited.

Once a person with MS has decided to use disease modifying treatments, the person may use the treatments for several years to several decades, as long as the person is tolerating the treatment. However, generally people will reach a stage in their personal disease course where disease modifying treatments no longer help. Thus, major questions of interest are whether or not disease-modifying MS drugs alter the natural history of the disease in the long-run and when to discontinue disease-modifying treatment. This review, in focusing on the discontinuation end of the time frame, will complement other efforts to establish comparative effectiveness and ranking of disease-modifying medical treatment to assist in answering the questions related to starting treatment.[8] The review will examine the long-term (greater than 3 years) consequences of discontinuing disease-modifying treatment by examining the long-term benefits and harms, and the reasons recorded for discontinuing treatment. Due to the long-term focus, we will concentrate on outcomes relevant to the patient for decisionmaking, such as relapse rates and changes in disability level, rather than intermediate outcomes. Magnetic resonance imaging to identify multiple sclerosis-related lesions has been shown to correlate with relapse rates in the shorter term, 6 months to 2 years.[7] However, long-term magnetic resonance imaging followup as surrogate marker for relapse rates or, more importantly, disease progression, currently lacks evidence, and so will not be an outcome in this review.

Since there are several disease modifying treatments available, people with MS may switch between different medications depending on tolerance, presence of adverse effects, or whether the current treatment is perceived to be helping. The pertinent clinical question for switching medications is what should the threshold level of disease activity be for recommending changing medications? This question is important, but qualitatively different than the question of when to stop disease-modifying treatments completely. To properly answer switching questions, a review will likely need to incorporate both short- and long-term research. Therefore, questions related to switching between disease modifying treatments are outside the scope of this review.

The review will also include a Key Question (KQ) aimed at understanding the evidence for patient values, beliefs, and preferences regarding discontinuation of disease-modifying drugs. Such information should support clinicians, patients, consumer advocates, and other decisionmakers in understanding the factors and processes that may contribute to a decision to discontinue treatment.

Given the lack of systematic reviews focused on long-term benefits and harms of disease modifying treatments, or patient preferences, this review will complement the existing systematic review literature on disease-modifying treatments. It will also contribute a common understanding of the state of the science of patient perspectives and preferences for discontinuing disease-modifying treatment.

II. The Key Questions

The draft Key Questions developed during AHRQ's topic Refinement process were posted for public comment from May 31, 2013, through June 30, 2013. The comments received represented a wide range of perspectives and suggested changes that would have altered the scope considerably and in incompatible directions. Specific suggestions added clarity to the included interventions and the timing of study followup. Our revised key questions and PICOTS are below:

KQ1: What are the consequences of discontinuing disease-modifying treatments in adult patients?
    a. What is the evidence for benefits for continuing versus discontinuing treatment?
    b. What is the evidence for long-term harms?
    c. What reasons for discontinuation of disease-modifying treatments have been reported in long-term observational cohort studies

KQ2: What are individual values, beliefs, and preferences regarding discontinuing disease-modifying drugs?
    a. What are patient and provider preferences for discontinuation of disease–modifying therapies?
    b. What are patient and provider preferences for participation in shared decisionmaking to discontinue disease-modifying therapies?

The draft PICOTS (**p**atients, **i**nterventions, **c**omparators, **o**utcomes, **t**iming, and **s**etting) are as follows:

- **Population(s)**
  - Adults with CIS, RRMS, SPMS, PPMS, or PRMS are included.
  - Pediatric patients with MS are excluded.

- **Interventions**
  - Disease-modifying treatments that may have been discontinued are provided in Table 1.

Table 1. Disease-modifying treatments

Generic (Administration)	Manufacturer (Trade Name)	FDA-Approved Indication	FDA Warnings
Interferon beta 1a (Injection)	• Biogen (Avonex®) • EMD Serono (Rebif®)	• May 17, 1996, for CIS and RRMS • March 7, 2002, for RRMS	• Yes • Yes
Interferon beta 1b (Injection)	• Bayer Healthcare Pharms (Betaseron®) • Novartis (Extavia®)	• July 23, 1993 • August 14, 2009, for CIS and RRMS	• Yes • Yes
Glatiramer acetate (Injection)	Teva (Copaxone®)	December 20, 1996, for RRMS	Yes
Natalizumab (IV)	Biogen (Tysabri®)	November 23, 2004, for RRMS	Yes, black box
Teriflunomide	Sanofi Aventis US (Aubagio) (leflunomide by Sanofi Aventis US as Arava for arthritis)	September 12, 2012 for RRMS	Yes, black box
Fingolimod/Oral	Novartis (Gilenya)	Sept 21, 2010, RRMS	Yes
Dimethyl fumarate/Oral	Biogen (Tecfidera)	March 27, 2013, RRMS	Yes

Abbreviations: CIS = clinically isolated syndrome; FDA = U.S. Food and Drug Administration; IV = intravenous; PRMS = primary progressive multiple sclerosis; RRMS = relapse-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

- Mitoxantrone is specifically excluded. This medication has a lifetime use limit, so ultimately discontinuing is not a choice.

- **Comparators**

- o Placebo
- o Disease-modifying treatments that may have been discontinued as in Table 1
- o Patients who did not receive disease-modifying treatments

- **Outcomes and Concepts/Topics of Interest**
  - o For KQ 1:
    - ■ Patient-centered benefits of disease-modifying treatments compared with baseline
      - □ Reduction in relapse rate (at least one relapse)
      - □ Change in disability
      - □ Change in the Expanded Disability Status Scale score (or other MS scales)
      - □ Progression of disease as determined by functional assessments
      - □ Time to sustained disease progression
    - ■ Intermediate outcomes such as immunological effects or MRI imaging changes are excluded
    - ■ Adverse effects of intervention(s)
      - □ Any reported adverse events
    - ■ Any reported reason for discontinuing treatment

  - o For Key Question 2:
    - ■ Empirical literature that will populate the conceptual framework provided in Figure 2
      - □ Individuals' attitudes, values, preferences for discontinuing treatments and related health states
      - □ Perceptions of risk and seriousness of health states
      - □ Factors and processes patients with MS use to evaluate the therapy and choice to discontinue it
      - □ Factors and processes patients with MS and clinicians use in shared decisionmaking
    - ■ Adherence to a treatment plan is excluded

- **Timing**
  - o For KQ 1, the duration of both treatment and followup must be over 3 years. Typical RCTs for MS efficacy or comparative effectiveness are 2 to 3 years. Since these drugs are intended for long-term use, possibly for decades, we are looking for studies that examine long-term use and long-term effects. However,
    - □ For studies that examined discontinuing DMT in women considering pregnancy or are pregnant the timing restriction will be relaxed.
    - □ For studies that examined discontinuing DMT in patients taking Natalizumab for purposes of drug holidays or changes in risk, the timing restriction will be relaxed.

- **Setting**
  - o Outpatient

III. Analytic Framework

Figure 1. Analytic framework for discontinuing disease-modifying treatments for Multiple Sclerosis
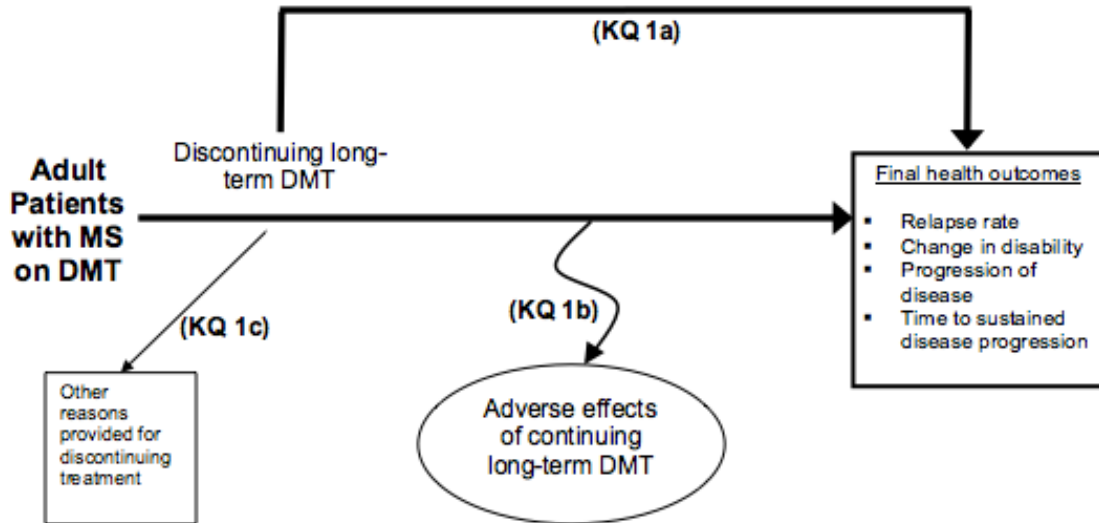

Figure 1 provides an analytic framework describing the treatment path and long-term benefits and harms of continuing versus discontinuing disease-modifying treatment.

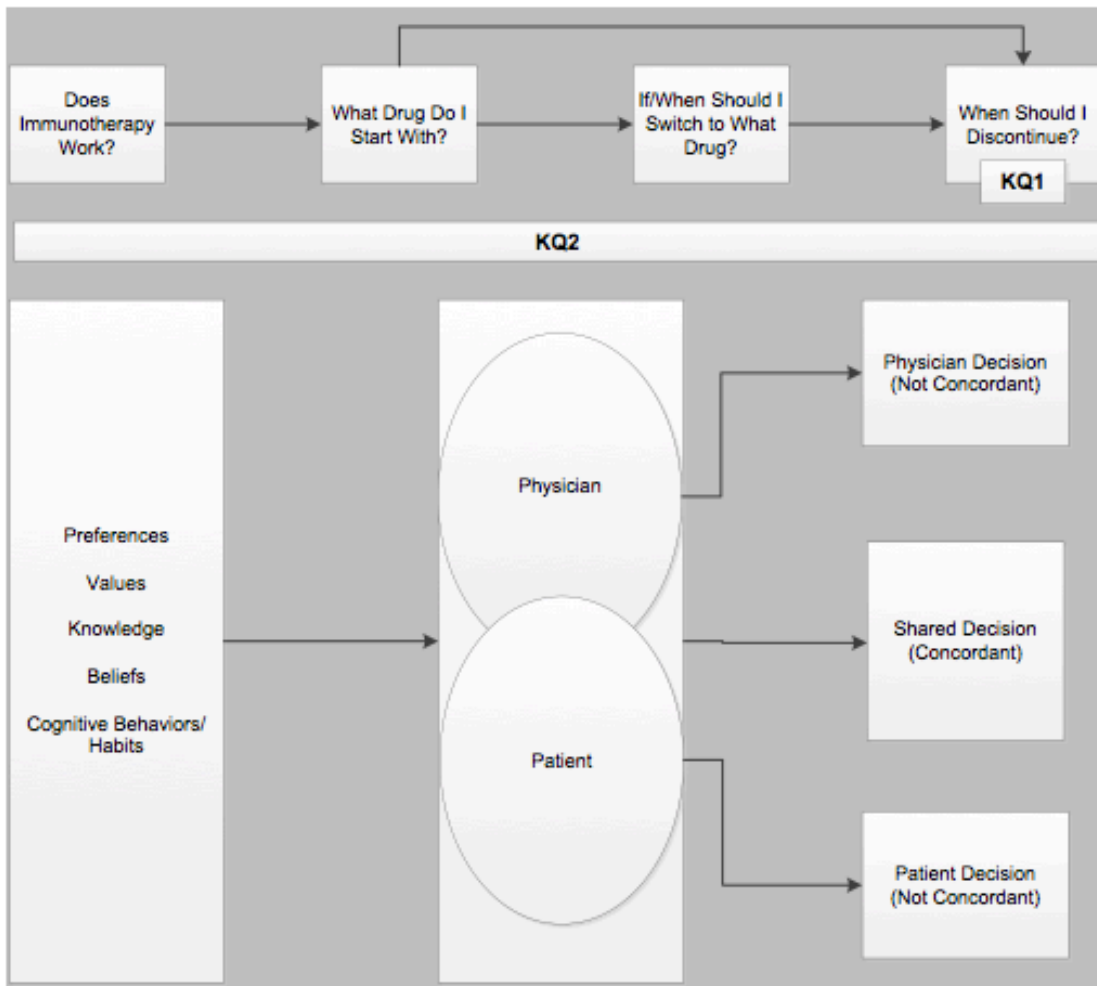**Figure 2. Draft conceptual framework for Key Question 2**

Figure 2 depicts at the top the logic path both physicians and patients must travel when considering disease-modifying treatments:

- Does it work?
- What drug should I start with?
- When should I switch a patient to a new drug and what should that drug be?
- When should a patient discontinue disease-modifying treatment?

This logic path creates the context within which patients and clinicians are making frequent decisions about disease-modifying treatment or, in the case of this review, the decision to discontinue. The lower part of the figure depicts the progression from an individual's internal decision context and process (such as preferences, values, knowledge, beliefs, and cognitive behaviors and habits) to an interpersonal decision context and processes between the physician and patient. The ovals representing the clinician and the patient overlap to represent that information which is shared between the two parties versus information and other cognitive processes that are held within only

the one individual. The level of overlap depends in part on the level of sophistication a patient brings to the decisionmaking process and in part on how well a physician understands a patient's beliefs, values, goals, and preferences. For example, a patient newly diagnosed with MS in the novice phase of learning about MS would likely have a smaller overlap.[10] Eventually, the interaction results in decisions that may or may not be concordant between the physician and patient.

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

Studies will be included in the review based on the PICOTS framework outlined in Section II and the study-specific inclusion criteria described in Table 2.

Table 2. Study inclusion criteria

Category	Criteria for Inclusion
Study Enrollment	Studies that enroll adults with CIS, RRMS, SPMS, PPMS, or PRMS
Study Design	RCTs, nonrandomized controlled trials, prospective and retrospective cohort studies, case control studies case series will be included for each population and treatment option.
Time of Publication	Search all literature 1990 forward. FDA-approved disease modifying drugs were only available after 1993.
Study Quality	All studies meeting inclusion criteria will be screened for eligibility. Studies that do not adequately report study information to allow the abstraction of time sequences for treatment and followup duration or have indeterminable numerators and denominators for outcomes and adverse event rates will be excluded.
Language of Publication	Although internationally-derived, given that literature on this topic published in English best represents interventions available and accessible in the United States, we will limit inclusion to studies with full text published in English. However, we will not limit our search so that potential language bias can be assessed.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

We will utilize bibliographic database searching to identify previous randomized controlled trials and observational studies published from 1990 to the present for studies enrolling adults with CIS or MS. Relevant bibliographic databases for this topic include MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), PsychInfo, and Scopus. Our preliminary search strategy appears in Appendix A. This search strategy employs relevant Medical Subject Headings and natural language terms to find studies on the topic. The concept search is supplemented with filters designed to select experimental designs. Bibliographic database searches will be supplemented with backward citation searches of highly relevant systematic reviews. We will update searches while the draft report is under public/peer review.

We will conduct additional grey literature searching to identify relevant completed and ongoing studies. Relevant grey literature resources include trial registries and FDA databases. We will search ClinicalTrials.gov and the International Controlled Trials Registry Platform (ICTRP). We will also review Scientific Information Packets (SIPs) sent by manufacturers of relevant interventions. Grey literature search results will be used to identify studies, outcomes, and analyses not reported in the published literature that may further inform findings for key questions. Since we do not anticipate finding RCTs

of sufficient length to be included in this review, we do not expect to be able to assess publication and reporting bias using the grey literature. The observational literature likely to be included rarely has protocols available to assess reporting bias.

We will review bibliographic database search results for studies relevant to our PICOTS framework and study-specific criteria. Search results will be downloaded to EndNote. Titles and abstracts will be reviewed by two independent investigators to identify studies meeting PICOTS framework and inclusion/exclusion criteria. All studies identified as relevant by either investigator will undergo full-text screening. Two independent investigators will screen full text to determine if inclusion criteria are met. Differences in screening decisions will be resolved by consultation between investigators and a third investigator if necessary. We will document the inclusion and exclusion status of citations undergoing full-text screening.

C. Data Abstraction and Data Management

Studies meeting inclusion criteria will be distributed among investigators for data abstraction and risk of bias assessment. One investigator will abstract relevant study, population demographic, and outcomes data. Data fields to be abstracted will be determined based upon proposed summary analysis. These fields will likely include author; year of publication; setting, subject inclusion, and exclusion criteria; and study design characteristics. For KQ1, we will also likely abstract intervention and control characteristics (intervention components, timing, frequency, duration); followup duration; participant baseline demographics; type of CIS or MS, MS severity; descriptions and results of outcomes and adverse effects; reasons for discontinuation; and study funding source. Studies that only report long-term benefits and harms aggregated across multiple drug-modifying treatments will not be abstracted. Such studies will be accounted for, however, in the article flow-diagram and references will be made available. For KQ2, we will also abstract study aims and study findings. Relevant data will be extracted into evidence tables. Evidence tables will be reviewed and verified for accuracy by a second investigator.

D. Assessment of Methodological Risk of Bias of Individual Studies

Risk of bias of eligible studies will be assessed using instruments specific to study design. We will assess risk of bias for randomized controlled trials, if found in the literature, using an instrument we develop based upon the Cochrane Risk of Bias tool.[11] The seven domains included in this tool include sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias (i.e., problems not covered by other domains). Specific study methodology or conduct will be used to judge potential risk of bias with respect to each domain following guidance in the Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0.[12] We will develop an instrument for assessing risk of bias for observational studies using the RTI Observational Studies Risk of Bias and Precision Item Bank.[12] We will select items most relevant in assessing risk of bias for this topic, likely including participant selection; attrition, detection, selective outcome reporting, and appropriateness of analytic methods. We will develop items for both risk-of-bias instruments to assess selective outcome and selective analysis reporting. Investigator assessment of these items will compare reported

results to planned analysis described in trial registries and/or the methodology section of the publication as described in a recent AHRQ Methodology report.[13]

Overall summary risk of bias assessments for each individual study will be classified as low, moderate, or high based upon the collective risk of bias inherent in each domain and confidence that the results are believable given the study's limitations. Investigators will consult to reconcile any discrepancies in overall risk of bias assessments. When agreement cannot be reached through consultation, a third party will be consulted to reconcile the summary judgment. Studies assessed with an overall high risk of bias will not be included in evidence synthesis due to the low confidence in study results. Information about these studies will be made available in appendices. We will qualitatively compare high risk of bias study results to synthesized evidence as a means of sensitivity analysis. Contradictions will be investigated in further depth.

E. Data Synthesis

For KQ1, we will summarize the results into evidence tables and qualitatively synthesize evidence for specific disease-modifying medications and unique population, length of study followup, and outcomes combinations. Studies will also be grouped by length of followup to examine changes over time, if any, in outcomes and reasons for discontinuing disease modifying treatments. We will use the best evidence of the available evidence provided by the identified observational literature.[14] Our exploratory literature search found no RCTs and significant numbers of observational studies, but many observational studies were found on preliminary examination to have high risk of bias. So while all identified articles will undergo abstraction, as noted in section C above, only the best evidence, based on those studies closest to an "ideal" study design,[15] that is, those studies with the lowest risk of bias, will be included in the evidence synthesis.

For KQ2, we will summarize the results into evidence tables and conduct a qualitative synthesis. We will group the literature by mapping the included studies to the conceptual framework (Figure 2) and analyze the study findings for emergent patterns for patient perspectives, clinician perspectives, and clinician/patient interpersonal interactions.

F. Grading the Strength of Evidence (SOE) for Individual Comparisons and Outcomes

The overall strength of evidence for select outcomes for KQ1 (relapse rate, change in disability, progression of disease, time to sustained disease progression) within each comparison will be evaluated based on four required domains: (1) study limitations (internal validity); (2) directness (single, direct link between intervention and outcome); (3) consistency (similarity of effect direction and size); and (4) precision (degree of certainty around an estimate).[16] A fifth domain, reporting bias, will be assessed when SOE based upon the first four domains is moderate or high.[16] Based on study design and conduct, risk of bias will be rated as low, medium, or high. Consistency will be rated as consistent, inconsistent, or unknown/not applicable (e.g., single study). Directness will be rated as either direct or indirect. Precision will be rated as precise or imprecise. Other factors that may be considered in assessing strength of evidence include dose-response relationship, the presence of confounders, and strength of association. Based on these factors, the overall evidence for each outcome will be rated as:[16]

- **High:** Very confident that estimate of effect lies close to true effect. Few or no deficiencies in body of evidence, findings believed to be stable.
- **Moderate:** Moderately confident that estimate of effect lies close to true effect. Some deficiencies in body of evidence; findings likely to be stable, but some doubt.
- **Low:** Limited confidence that estimate of effect lies close to true effect; major or numerous deficiencies in body of evidence. Additional evidence necessary before concluding that findings are stable or that estimate of effect is close to true effect.
- **Insufficient:** No evidence, unable to estimate and effect, or no confidence in estimate of effect. No evidence is available or the body of evidence precludes judgment.

G. Assessing Applicability.

Applicability of studies will be determined according to the PICOTS framework. Study characteristics that may affect applicability include, but are not limited to, type of CIS or MS, unobserved differences in patient preferences, or country within which treatment is provided, given differences in international regulations and treatment preferences.[17]

V. References

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VI. Definition of Terms

Not applicable

VII. Summary of Protocol Amendments

Not applicable

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role

as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodologic experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published 3 months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest which cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

Appendix A. Preliminary Search Algorithms

For KQ1, we will search Medline via Ovid, Cochrane Libraries, and Scopus, modifying the Medline searches for the other databases.

KQ1. MS/Drug Holiday:
Database: Ovid MEDLINE
Search Strategy:

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1   exp multiple sclerosis/dt, th, im
2   drug holiday$.mp.
3   discontinu$.mp.
4   halt$.mp.
5   cessat$.mp.
6   interrupt$.mp.
7   stop$.mp.
8   2 or 3 or 4 or 5 or 6 or 7
9   1 and 8

KQ1. MS/Immunomodulation:
Database: Ovid MEDLINE(R)
Search Strategy:

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1   exp multiple sclerosis/dt, th, im (16589)
2   exp immunomodulation/ (229961)
3   exp immunosuppressive agents/ (235978)
4   exp immunologic techniques/ (1168203)
6   1 and 2 (1184)
7   1 and 3 (1831)
8   1 and 4 (2881)
9   6 or 7 or 8 (4864)

KQ1. MS/Drug Names:
Database: Ovid MEDLINE(R)
Search Strategy:

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1   Multiple Sclerosis, Relapsing-Remitting/dt, im, th [Drug Therapy, Immunology,
    Therapy]
2   exp Interferon-beta/
3   interferon beta.mp.
4   glatiramer acetate.mp.
5   natalizumab.mp.
6   teriflunomide.mp.
7   3 or 4 or 5 or 6
8   1 and 7
9   limit 8 to (addresses or autobiography or bibliography or biography or classical article
    or comment or editorial or historical article or interactive tutorial or lectures or news
    or newspaper article or patient education handout)
10 8 not 9
11 limit 10 to (english language and humans and yr="1990 -Current")

For KQ2, we will search Medline via Ovid, Cochrane Libraries, PsychInfo, and
CINAHL, modifying the Medline searches for the other databases.

KQ2. MS/Patient Preference:
Database: Ovid MEDLINE(R)
Search Strategy:

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1   exp multiple sclerosis/dt, th, im
2   exp patient preference/
3   exp attitude to health/
4   exp physician-patient relations/
5   exp decision making/
6   exp choice behavior/
7   exp decision support techniques/
8   exp personal autonomy/
9   exp patient participation/
10   decision making.mp.
11   decision support.mp.
12   risk communication$.mp.
13   shared decision$.mp.
14   2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15   1 and 14
16   exp health knowledge, attitudes, practice/

17   exp *multiple sclerosis/
18   16 and 17
19   15 or 18
20   exp multiple sclerosis/px
21   14 and 20
22   19 or 21