April 2015

Treatment of Multiple Sclerosis: Meeting Summary

About PCORI

PCORI is committed to transparency and a rigorous stakeholder-driven process that emphasizes patient engagement. PCORI uses a variety of forums and public comment periods to obtain public input to enhance its work. PCORI helps people make informed healthcare decisions and improves healthcare delivery and outcomes by producing and promoting high-integrity, evidence-based information that comes from research guided by patients, caregivers, and the broader healthcare community.

PCORI was authorized by the Patient Protection and Affordable Care Act of 2010 as a nonprofit, nongovernmental organization. PCORI's purpose, as defined by the law, is to help patients, clinicians, purchasers, and policy makers make better-informed health decisions by "advancing the quality and relevance of evidence about how to prevent, diagnose, treat, monitor, and manage diseases, disorders, and other health conditions."

Patient-Centered Outcomes Research Institute
1828 L St., NW, Suite 900
Washington, DC 20036
Phone: (202) 827-7700
Fax: (202) 202-355-9558
Email:info@pcori.org

Follow us on Twitter: @PCORI

Contents

I. Executive Summary

On April 2, 2015, PCORI held a meeting, Prioritizing Comparative Effectiveness Research Questions for the Treatment of Multiple Sclerosis: A Stakeholder Workshop, in Washington, DC. The purpose of this workshop was to identify, refine, and prioritize comparative effectiveness research questions about the treatment of multiple sclerosis. Participants in this multi-stakeholder workshop discussed both whether there are patient-centered comparative effectiveness research questions that PCORI should pursue and what those questions might be. Forty-three invited stakeholders attended in person. The meeting was open to the public via teleconference and webinar.

PCORI identified organizations to participate based on their representation of key stakeholder groups involved in the treatment of multiple sclerosis, including patients, patient advocacy groups, clinicians, researchers, the pharmaceutical and biotechnology industry, and payers (insurance providers or employers). Before the workshop, invited participants were requested to propose comparative effectiveness research questions about the treatment of MS and were offered specific guidance for doing so, called "How to Write a Practical & Useful Research Question."

PCORI staff grouped the questions submitted into four categories: Comparison of DMTs, including differential effects in subgroups; Care strategies; Non-pharmacologic and non-DMT therapy for specific symptoms and overall health; and Timing of therapy and study design. PCORI staff refined the stakeholders' inputs and drafted representative "straw man" questions in each category. These questions were discussed and revised by the participants during breakout sessions at the workshop, resulting in 13 questions.

Related Information

- MS Stakeholder Workshop Meeting Materials

In the plenary session that followed the breakout meetings, the leader of each group presented the 13 questions to all the participants (see Appendix). These questions were discussed, and other comments about the treatment of MS were offered.

In a post-meeting survey, the participants ranked their top 6 of the 13 questions. The results of that ranking exercise yielded the following questions as top five priorities:

- What are the comparative benefits and harms of non-pharmacological and pharmacological approaches in relation to key symptoms (e.g., emotional health, fatigue, cognition, pain) in people with MS?
- In people with progressive MS, what is the comparative effectiveness of different care delivery approaches (i.e., MS specialty center vs. community neurology; direct care vs. telemedicine; "specialized medical home" vs. community neurology delivery of care) in improving outcomes such as functional status, quality of life, symptoms, ER use, and hospitalization?
- Does an integrative model of care along with DMT in a newly diagnosed individuals affect disability progression and symptoms (physical, emotional and cognitive) compared to treatment with DMT alone?
- Among MS patients receiving a DMT who experience disease activity, what are the benefits

and harms of continuing the same therapy versus changing to a new medication?

- What are the comparative benefits and harms of different disease-modifying therapies in newly diagnosed relapsing, remitting multiple sclerosis on disease activity, disease progression, symptoms, and quality of life?

II. Background

Multiple sclerosis (MS) is a chronic condition of the central nervous system characterized by damage to the myelin sheaths that cover and protect nerves, resulting in fatigue, numbness, visual disturbances, bladder problems, mobility issues, and more. Approximately 400,000 Americans have MS. Most patients are diagnosed between 20 and 40 years of age, and there is a strong female predisposition. The clinical course is highly variable, generally unfolding over decades, and symptoms range from mild to the development of severe disability.

The number of specific treatments for MS, commonly referred to as "disease-modifying therapy" (DMT) has increased dramatically since the mid-1990s. There are now 12 such DMTs approved by the FDA for use in the relapsing-remitting form of MS.

Various stakeholders that are involved with MS have expressed a high degree of interest in comparative effectiveness research (CER) in MS, and based on this interest, PCORI commissioned a topic brief for consideration by its Assessment of Prevention, Diagnosis, and Treatment Options Advisory Panel in January 2014. PCORI also included the treatment of MS as a topic in three rounds of requests for applications for its Pragmatic Clinical Studies program, during the period from June to October 2014, resulting in 11 letters of intent but no invitations to submit a research application. The main reasons for PCORI's decision not to invite an application were small sample sizes, lack of sufficiently-detailed data in observational studies, comparators that were not compelling, and clinical trial outcomes that were not patient-centered.

Based on this expressed interest and discussions with individual stakeholders, PCORI held three preliminary, small stakeholder workshops on October 30, 2014; January 29, 2015; and January 30, 2015. The latter two were directed at the pharmaceutical and biotechnology industry and payers, respectively. Given the level of interest, PCORI then proceeded to plan the large multi-stakeholder workshop summarized herein.

PCORI identified organizations to participate based on their representation of key stakeholder groups involved in the treatment of multiple sclerosis, including patients, patient advocacy groups, clinicians, researchers, the pharmaceutical and biotechnology industry, and payers (insurance providers or employers). Before the workshop, the invited stakeholders were asked to propose CER questions about the treatment of MS for discussion during the workshop. PCORI staff grouped the questions into four categories: Comparison of DMTs, including differential effects in subgroups; Care strategies; Non-pharmacologic and non-DMT therapy for specific symptoms and overall health; and Timing of therapy and study design. While all groups were asked to consider study design, Group 4 was asked to

delve into it more fully.

PCORI staff refined the stakeholders' inputs and drafted representative questions in each category for the breakout sessions. These questions were used to stimulate discussion and were revised and others added, and then the questions were ranked by the participants at the breakout sessions.

Topic	Number of Questions Submitted
Comparison of DMTs, including differential effects in subgroups	17
Care strategies	14
Non-pharmacologic and non-DMT therapy for specific symptoms and overall health	22
Timing of therapy and study design	7

III. Introductory Remarks

Dr. Joe Selby, PCORI's Executive Director, welcomed the workshop participants. He reviewed PCORI's mandate to assist patients, clinicians, purchasers, and policy-makers in making informed health decisions by generating useful evidence. He discussed PCORI's involvement with the MS community and comparative effectiveness research on MS, including naming it as a topic for its Pragmatic Clinical Studies program. He noted that the workshop includes a broad range of stakeholders. In addition to the in-person attendees, more than 40 people participated via webinar and teleconference. He stated that the purpose of the workshop was to identify, refine, and prioritize comparative effectiveness research questions about the treatment of multiple sclerosis.

Dr. Selby explained that most of the workshop would be focused on the breakout groups, which are charged with developing the research questions that PCORI will consider for a possible funding announcement. He stated that the workshop deliberations were advisory and that PCORI would take the comments and recommendations from the workshop participants, perform further queries to determine the value and feasibility of pursuing proposed research questions, and consult with PCORI's Science Oversight Committee. PCORI's Board of Governors would ultimately decide on the disposition of a possible funding announcement. He reminded the attendees that the proceedings were being webcast and would be archived on the PCORI website.

Dr. David Hickam, PCORI's Program Director for Clinical Effectiveness Research, gave an introduction to the goals of clinical comparative effectiveness research and PCORI's current CER portfolio. He noted that CER should be a public good that gives health care decision makers – patients, clinicians, purchasers and policy makers – access to the latest open and unbiased evidence-based information about treatment options and informs choices and is closely aligned with the sequence of decisions patients and clinicians face.

Dr. Steve Clauser, PCORI's Program Director for Improving Healthcare Systems, gave an introduction to his program's approach to CER, funding research questions that address innovative use of technology (e.g., telehealth and patient self-care); novel deployment of health personnel

(e.g., interdisciplinary care teams and care transitions); and redesign of organizational health care models (e.g., collaborative care for comprehensive psychosocial care or symptom management).

Dr. Diane Bild, Senior Program Officer in PCORI's Clinical Effectiveness Research Program described PCORI's engagement with the research community and other stakeholders in MS. PCORI included "Treatment options for patients with MS" as a topic in three rounds of receipt of letters of intent (LOI) for its Pragmatic Clinical Studies program and received 11 LOIs in response. Six were for observational studies, and five were for clinical trials but none were invited to submit because of small sample sizes, lack of sufficiently-detailed data in observational studies, comparators that were not compelling, or outcomes that were not patient-centered.

Because of the strong interest in MS, PCORI held three small stakeholder meetings on October 30, 2014 and January 29 and 30, 2015. The first included two patients and representatives from the MS Society, the American Academy of Neurology, the VA Centers of Excellence in MS, and the National Institute on Neurological Disorders and Stroke. The second meeting focused on the pharmaceutical and biotechnology industries, and the third meeting focused on payers. These groups identified a set of challenges to the conduct of CER, including a lack of consensus on metrics for measuring markers of MS activity that align with symptoms, the large number of available treatment options, large variability in symptom presentation and clinical course, large variability in treatment preferences among physicians and patients, the long natural history of disease, and reluctance of patients and clinicians to enroll in randomized clinical trials. Nevertheless, these groups generally expressed that there was high value in generating more evidence for patients and clinicians to use to make choices about the treatment of MS.

Dr. Bild then provided instructions about the conduct of the breakout groups. She reminded everyone of the materials that were provided, including a narrative review from Duke on comparative effectiveness of treatment of symptoms in MS; a set of instructions for writing a CER question; sets of questions for each breakout group; a set of the original questions with background, as submitted by the workshop participants; a roster of workshop participants; and copies of the slides presented in the morning session.

The four groups, and their leaders and PCORI facilitators were:

1. Comparison of DMTs, including differential effects in subgroups -- Drs. Aaron Miller and Anne Trontell
2. Care strategies – Drs. Alex Race-Grant and Steve Clauser
3. Non-pharmacologic and non-DMT therapy for specific symptoms and overall health – Drs. Heidi Maloni and David Hickam
4. Timing of therapy and study design – Drs. Ursula Utz and Joe Selby

IV. Breakout Sessions

Participants in each breakout session were given approximately three hours and instructed to develop up to four CER questions for presentation at the final plenary session. A summary of each Breakout Session is provided, including the question that was developed along with discussions about the topic represented by each question.

Group 1: Comparison of DMTs, including differential effects in subgroups

Breakout leader: Dr. Aaron Miller, Professor of Neurology, Icahn School of Medicine at Mount Sinai
PCORI staff facilitator: Dr. Anne Trontell, Senior Program Officer, Clinical Effectiveness Research Program

Group members:

- Ms. Alissa Ayden, Support Groups and Outreach Manager, Multiple Sclerosis Foundation
- Dr. Lynn Hudson, Chief Science Officer, Critical Path Institute
- Dr. Laura Julian, Medical Science Director, Genentech
- Dr. John Marler, Medical Officer, Food and Drug Administration
- Dr. Áine Miller, Senior Director, Regulatory Affairs, Alkermes
- Dr. Michael Panzara, Group VP, Therapeutic Area Head, Multiple Sclerosis and Neurology, Genzyme
- Ms. Nancita Rogers, Consultant, MS Society
- Ms. Sara Traigle van Geertruyden, Partner, Thorn Run Partners, PIPC

PCORI staff:

- Ms. Jana-Lynn Louis, Program Associate, Clinical Effectiveness Research
- Ms. Kimberly Bailey, Engagement Officer, Clinical Effectiveness Research
- Dr. Layla Lavasani, Program Officer, Clinical Effectiveness Research

The group discussed the straw man questions, which included comparing the benefits and harms of treatment with DMTs and of switching DMTs. The group emphasized the importance of patient preferences and tolerance of drug side effects, which influence treatment recommendations and choices. Important concerns included specifying appropriate and measurable treatment outcomes, the difficulty of conducting clinical trials because of clinician preferences for use of specific medications and the ethics of randomizing to placebo controls, the general difficulty enrolling patients in clinical trials of DMTs, and the challenge of studying the large number of medications now available for MS. The group reviewed the questions that had been proposed by the workshop participants. Questions comparing the specific effects of DMTs were deemed very difficult to answer, particularly examining the effects on demyelination. Questions about the risks of treatment could be studied by using registries. The group proposed adding specific endpoints to several of the questions. A new question was raised about studying the perceived impact of smoking in people with MS.

Based on the discussions, the group formulated the following questions:

Group 1 - Question 1. What are the comparative benefits and harms of different disease-modifying therapies in newly diagnosed relapsing, remitting multiple sclerosis on disease activity, disease progression, symptoms, and quality of life?

The group discussed the need for information on comparative benefits and harms of therapies in order for patients to choose among DMTs, which includes understanding patient preferences and tolerance of drug side effects. Studies must identify and incorporate

outcomes that are clinically important to physicians and meaningful to patients. The group discussed whether to focus on newly-diagnosed or secondary progressive MS patients, the variability in insurance coverage for various treatments, the challenge of consenting patients to participate in randomized trials, the large number of drugs available, the challenges to designing a robust, methodologically sound observational study, and the need for a long duration (10+ years) to adequately capture disease progression and meaningful quality of life measures and other outcomes.

Group 1 - Question 2. Among MS patients receiving a DMT who experience disease activity, what are the benefits and harms of continuing the same therapy versus changing to a new medication?

The group discussed the need to define disease activity using a combination of non-minimal clinical and MRI disease activity. It was noted that NEDA (no evidence of disease activity) may be a key outcome for MS patients and that EDSS (expanded disability status scale) components can be problematic to obtain and highly variable over time. The group recommended focusing on oral drugs rather than injectable drugs, since few patients remain on injectable drugs for substantial period of time. Insurance coverage may require patients to "fail first," which may not constitute optimal clinical management. One might be able to randomize patients to a new treatment vs. remaining on the current treatment for a study when an unacceptable disease activity threshold is achieved. In these cases, there may be equipoise among patients and clinicians. It was noted that there is a high degree of variability of clinician practice regarding when to recommend switching treatments to their patients.

Group 1 - Question 3. Is treatment escalation using DMTs as effective as starting treatment with higher efficacy treatments in early active, previously untreated patients?

The group discussed the need for definitions for higher efficacy and early treatment that the study would need to be many years in duration, and that blinding of arms would be difficult due to medication side effects.

The following two questions also emanated from the previous discussion:

Group 1 - Question 4. What is the comparative effectiveness of smoking cessation efforts upon disease activity, progression, symptoms, and quality of life in MS?

Group 1 - Question 5. What is the comparative effectiveness of stopping versus continuing therapy after a period of prolonged disease stability in patients with MS?

Group 2: Care strategies

Breakout leader: Dr. Alex Rae-Grant, Staff Neurologist, Mellen Center for Multiple Sclerosis
PCORI staff facilitator: Dr. Steve Clauser, PhD, MPA, Program Director, Improving Healthcare Systems

Group members:

- Dr. Naomi Aronson, Executive Director, Blue Cross Blue Shield Association
- Ms. Natalie Blake, Director of Programs and Services, MS Foundation
- Dr. Meg Frazer, Senior Director, Pfizer Medical Affairs, Pfizer Inc
- Dr. Sanjay Gandhi, Senior Director, Global Health Economics and Outcomes Research, Teva Pharmaceuticals
- Mr. Andrew Hu Senior Director, Policy and Research, PhRMA
- Ms. Laura Kolaczkowski, Lead Patient Representative, ¡ConquerMS
- Mr. Joe Laferrera, Partner, Gesmer Upgrove LLP
- Mr. Dylan Nelson Analyst, National Business Group on Health
- Dr. Susan Oh, Assistant Director of Pharmacy Affairs, American College of Physicians
- Dr. Gilmore O'Neill, Vice President, MS Research & Development, Biogen Idec
- Dr. Kelly Pokuta, Director, Catamaran, Pharmaceutical Care Management Association
- Dr. Mark Rametta Deputy Medical Director, Hematology/Neurology, Bayer Pharmaceuticals
- Dr. Tom Simpatico, Chief Medical Officer, Department of Vermont Health Access

PCORI staff:

- Ms. Fatou Ceesay, Program Associate, Clinical Effectiveness Research
- Dr. Stanley Ip, Senior Program Officer, Clinical Effectiveness Research

The group began with a high level discussion about what one could do to help people with MS without "removing the diagnosis." Important concerns included the need for better understanding of cognitive impairment in MS and the importance of cognitive assessment as part of general evaluation; how to truly engage and empower patients in their care and determine what matters to them; the need to identify and use disease measures for fatigue, employment, quality of life, and general function; the need for measurement tools that work across disease populations; the need for prognostic predictors; the importance of brain atrophy; the effect of adherence to treatment on disease progression; the need to improve understanding about available treatment options; better monitoring of disease activity and symptoms; and how employers might support people with MS and help them remain employed and productive. Another important issue is the affordability of treatments by patients. Finally, support for care providers is an important concern.

The group formulated the following questions:

Group 2 - Question 1: In people with progressive MS, what is the comparative effectiveness of different care delivery approaches (i.e., MS specialty center vs. community neurology; direct care vs. telemedicine; "specialized medical home" vs. community neurology delivery of care) in improving outcomes such as functional status, quality of life, symptom measurements, ER use, and hospitalization?

The group offered the premise that it is not clear how best to organize care and discussed whether outcomes are better when the patient is cared for by a specialist or a generalist; comparing outcomes of patients treated by Accountable Care Organization (ACO) vs. other care models; the durability of the ACO model (and whether it will still exist in five years); and the lack of updated and consistent guidelines

across care organizations. The group considered several viable comparisons, including treatment in an MS specialty center vs. community neurology, local vs. distance treatment, direct treatment vs. telemedicine, patient-centered medical home vs. "specialized medical home" care vs. community neurology delivery of care. The group recommended that outcomes be measured by common tools that incorporate measures such as disability, adherence to treatment, quality of life, symptoms, emergency department and hospital use over a long period. Factors such as location, regional variation, access to care, ethnic disparities (particularly whether minorities with MS fare worse than whites), employment, and scalability are important considerations.

Group 2 - Question 2: In people with relapsing MS within 2 years of diagnosis, what is the comparative effectiveness of changing DMT using a NEDA strategy (no relapse, no new MRI or enhancing lesion, no change in disability) vs. not changing DMT in terms of functional status, quality of life, symptom measurements, ER use, and hospitalization?

There are no data or evidence to support and little consensus among clinicians to guide when treatment with DMTs should be altered. The group discussed the impact of difficulty obtaining some medications for some patients, adverse side effects of medication, and the impact of specific symptoms on the decision to change medication. The population studied should include people with highly active disease, to provide the ability to observe useful outcomes within five years. Other issues included differences between clinical and symptomatic progression, difficulty controlling for many confounding variables, the need for patient-reported outcomes, and defining the treatment objective. One must be able to tease apart disease-specific symptoms from co-morbidity or aging-related symptoms when defining treatment success or failure. The group discussed the value of NEDA, as well as study timing and feasibility.

Group 2 - Question 3: In people with relapsing MS, what is the comparative effectiveness of physician-directed vs. allied health-directed vs navigator-directed, vs technological-enabled self-management tools for improving initial decision making, patient care experiences, decision regret, quality of life and adherence to therapy?

The group discussed the feasibility of addressing this research question and the likely durability of the information obtained. The group stated that addressing this question was feasible and that the results would be implementable and wouldn't require a transformation of the healthcare system. The group questioned how often instructions for patients are standardized and whether missed dosing is a significant problem in MS, as it is for other conditions. There is a lack of trust for pharmaceutical companies and healthcare management companies. It was remarked that it would be helpful to study methods for engaging patients, comparing self-management tools that have been tested and shown to be efficacious – for example, using certified patient navigators or "information dumping" vs. using a personalized information delivery tool. Patients are not often given the opportunity for shared decision making. Shared decision making could be compared with usual education efforts, nursing educators, patient navigators, educational sessions, or other technologies. Outcomes should include patient satisfaction, decision regret, quality of life and adherence to therapy over two years. Other considerations include the study of ethnic disparities in MS, comparing more vs. less aggressive therapy. There is an assumption that MS is more aggressive among ethnic minorities, which may be due, at least in part, to differences in access to care or information.

Group 3: Non-pharmacologic therapy for specific symptoms and overall health

Breakout leader: Dr. Heidi Maloni, National Clinical Nursing Director, MS Center of Excellence, VHA
PCORI staff facilitator: Dr. David Hickam, Program Director, Clinical Effectiveness Research

Group members:

- Dr. Virgil Mathiowetz, Associate Professor, American Occupational Therapy Association
- Dr. Deborah Backus, Director, MS Research, American Physical Therapy Association
- Ms. Kathy Costello (who replaced Tim Coetzee), Vice President, National MS Society
- Dr. Emmeline Edwards, Director, Division of Extramural Research, National Center for Complimentary and Integrative Health
- Dr. Jennifer Graff, Vice President, Comparative Effectiveness Research, National Pharmaceutical Council
- Ms. Debra Madden, Patient Advocate/HIT Project Manager, Independent Research Advocate
- Ms. Wendy Nickel, Director, Center for Patient Partnership in Healthcare, American College of Physicians
- Ms. Becky Schierman, Director, Quality Improvement, American Academy of Neurology
- Dr. Matthew Sorenson, Associate Professor, Association of Rehabilitation Nurses

PCORI staff:

- Ms. Julie McCormack, Program Officer, Clinical Effectiveness Research
- Dr. Danielle Whicher, Program Officer, Clinical Effectiveness Research

The group noted that many of the questions submitted by participants were overlapping. They discussed uncertainty about whether complementary and alternative treatments would provide people with MS with more of a sense of control over their clinical path than pharmacological therapy. The group noted that there are different types of MS that should be studied in separate trials (e.g., people with primary progressive MS and people with secondary progressive MS). The group also noted the wide variety of measures that could be used to study QOL (EUROQOL, NIH toolbox, PROMIS) and other important patient-centered outcomes. The group commented on the limited evidence as outlined in the Duke narrative review that was distributed before the workshop and stated that evidence generation in this area will likely occur through the conduct of several moderately sized studies. They recommended consistency in the conduct of studies to enable later comparisons across studies and meta-analyses. There was concern about the ability to standardize different therapies (e.g., yoga) across different locations because there may be a lack of consensus standards available.

The group proposed and discussed the following questions:

Group 3 - Question 1: Does an integrative model of care along with DMT in a newly diagnosed individuals affect disability progression and symptoms (physical, emotional and cognitive) compared to treatment with DMT alone?

Group 3 - Question 2: What are the comparative benefits and harms of non-pharmacological and pharmacological approaches in relation to key symptoms (e.g., emotional health, fatigue, cognition, pain) in people with MS?

Group 3 - Question 3: What are the comparative benefits and harms of specific dietary regimens in people with MS?

The group discussed what constituted important outcomes, including change in cognitive or physical disability, pain, fatigue, function, and QOL. It was noted that mood and depression are closely related to cognition and that, in general, cognition has been poorly studied. The group classified symptoms into three categories: physical, cognitive, and mood. Several group members noted that the ultimate or most important outcome measure is likely cognitive and physical disability. It was also noted that at certain levels of disability (i.e., severe disability), it may be difficult to see a change over the course of the study, so other outcomes may be more important in this context.

The group also discussed the nature of non-pharmacologic interventions and agreed that it is unlikely that a study would compare complementary and alternative medicine (CAM) to pharmacological treatment. Instead, a study should compare DMTs plus some complementary therapy to DMTs alone. Comparisons could also be made across degrees or intensity of interventions or modes of delivering the same intervention (e.g., in-person, group treatment, by phone, or via internet.) The group considered where the most significant evidence gaps are, whether comparing different types of CAM to each other or comparing CAM to some other type of treatment. One gap proposed is whether people with MS should be treated early in the course of disease with CAM to delay progression or whether CAM should focus on patients with more advanced disease, which is current practice. The group considered a more integrated model of care that includes elements of education, nutrition and exercise, and physical and cognitive therapy. The goal would be to see if this model of care delays disease and symptom progression. The comparators would be an integrated care model (which would include treatment with DMTs) vs. DMTs alone for newly diagnosed patients. The group expressed concerns about whether delivery systems would incorporate this model and agree to pay for this intervention for people in the research study and whether an integrative care model could be widely implemented. It was mentioned that the National MS society already has a program in this area, so there may be an opportunity to co-fund a study.

Group 4: Timing of therapy and study design

Breakout leader: Dr. Ursula Utz, Program Director, NIH/National Institute of Neurological Disorders and Stroke
PCORI staff facilitator: Dr. Joe Selby, Executive Director, PCORI

Group members:

- Dr. Thorsten Eickenhorst, Senior Vice President and Chief Medical Officer, EMD Serono

- Dr. Suchitra Iyer, Project Officer, Agency for Healthcare Research and Quality
- Dr. Laurie Lincoln, Director, Pharmaceutical Care Programs, Alliance Community of Health Plans
- Dr. Robert McBurney, Chief Executive Officer, Accelerated Cure Project for Multiple Sclerosis
- Dr. Phil Posner, Professor, Retired, MS Society
- Dr. Carrie Sammarco, Nurse Practitioner, NYU Multiple Sclerosis Center
- Dr. Rahul Sasane, Executive Director, Health Economics and Outcomes Research, Novartis Pharmaceuticals
- Ms. Kristin Viswanathan, Manager, Reimbursement and Health Policy, Biotechnology Industry Organization

PCORI staff:

- Ms. Jess Robb, Program Associate, Clinical Effectiveness Research
- Dr. Diane Bild, Senior Program Officer, Clinical Effectiveness Research

The group discussed the need to define time frames for treatment for a specific study, the effects of DMTs on symptoms and in the setting of comorbid conditions, and the lack of FDA-approved drugs for primary progressive MS. An important decision that patients with secondary progressive MS face is whether to stop DMTs. Because of the lack of FDA-approved treatments in this setting, physicians code these patients as having relapsing MS. Physicians are making decisions based on limited knowledge. In any observational study, one must be concerned that treatment type for some patients may be associated with less adherence or unhealthier lifestyles that confound the association between the treatment and the outcome. For example, those with less access to care have poorer outcomes that could be attributed to lower use of DMTs or unhealthier life habits.

A trial that seeks to study whether a more aggressive approach works must be able to identify subgroups to test whether there are groups that benefit. A key question is whether we can identify a subgroup of patients in whom delaying therapy would be beneficial or at least not harmful, given the trade-offs of drug treatment. It is possible that in a large study, data could be collected, including biomarker data, to identify such subgroups. PCORI would emphasize the use of markers that have been proposed or promoted for clinical care.

Outcome measures must consider impairment as well as disability. The MS Outcomes Assessment Consortium (MSOAC, part of the Critical Path Institute) is moving towards new outcomes measures that capture the patient perspective. The group discussed that rather than wait for consensus outcomes measures to be identified, funders would expect investigators to provide rationale, and defend what they propose.

Observational studies suffer from selection bias, which must be addressed. These include factors that influence how initial treatment is determined, as well as how decisions are made to switch, escalate, or stop treatment. Another issue is that it isn't clear how treatment failure should be defined. The group discussed the need for large studies to identify small effects associated with specific therapies. One stance expressed is that only very large effects, or "actionable" results – therapies that are associated with odds ratios of 5 or more – are of interest. Identifying these effects would not require large sample sizes. Another issue with observational studies, particularly registries, is whether they include appropriate outcomes. The consensus was that some registries do include them.

It was clarified that if PCORI issued a PFA, the applicant would be required to justify any and all

measures proposed and to address issues of selection bias and other confounding in any proposed observational study.

Group 4 - Question 1. What are the benefits and harms of early vs. delayed treatment with DMTs, in terms of symptoms, function, QOL, and disease activity in treatment-naïve, recently-diagnosed patients (meeting McDonald criteria within 12 months)?

The group discussed the importance of identifying subgroups that would benefit from different strategies and of identifying the appropriate cohort for an observational study of this question. It would be difficult to conduct an RCT of this question, because there is a general consensus that early aggressive treatment is better than delayed treatment, and there is evidence that early treatment reduces relapse rates. However, the risks and benefits of this approach are note fully known and if there is a particular subgroup of patients that benefits more from early treatment. The group noted that timing should be defined based on time of diagnosis, since it is not known when disease onset actually occurs. Timing could represent a range of options, not just a dichotomous variable (early vs. late). It was suggested that there could be natural experiments available to test this, with the Affordable Care Act now providing access to treatments to patients who previously did not have them.

The idea of including children was considered, but the group concluded that that would introduce too much complexity.

Group 4 - Question 2. In patients who recently transitioned from relapsing to progressive MS or were recently diagnosed with SPMS, what are the benefits and harms of continuing compared to discontinuing DMTs on outcomes including but not limited to symptoms, QOL, function, disease activity, disability, and/or mortality?

The group discussed the value of having consistent outcomes across studies to facilitate meta-analyses, the difficulty in defining when MS has transitioned from relapsing to progressive, and the fact that this question may become less relevant after the results of the ASCEND trial, which is studying the effects of natalizumab in patients with secondary progressive MS. Results are expected in 2017.

The group commented that studies should include both patient reported outcomes and economic outcomes. A key issue is that secondary progressive MS is a retrospective assessment. Also, physicians are wary of diagnosing it because of the lack of established treatment and fear that payers will not reimburse for its treatment, although others commented that denial of coverage in this circumstance is rare. One resource mentioned was NARCOMS, a registry of MS patients. Caution was generally urged, however, because of selection bias and lack of information about non-participants, high turnover, and lack of longitudinal data in some registries. There do not currently seem to be classic cohort studies in MS that would address these concerns.

Study designs: What are the advantages and disadvantages of clinical trials that focus on a specific subset of populations, interventions, and outcomes vs a larger, more comprehensive large observational study?

The group mentioned concerns about the ethics and feasibility of placebo-controlled RCTs in the study of DMTs. One would need to identify clinical situations where equipoise exists. One such situation might be initiation of therapy shortly after diagnosis vs. delaying therapy. Otherwise, RCTs comparing specific treatments for specific conditions would be appropriate.

Some believed strongly that only an observational study design was feasible for most research questions. They thought that natural experiments with differential levels of care for MS might be valuable. This could include comparisons among countries where treatment guidelines differ, among different Medicaid programs, or based on other instances where populations differ based on access to care. Careful attention would need to be paid to confounding.

V. Plenary session: Discussion of Prioritized CER Questions and General Discussion

Bryan Luce, PCORI's Chief Science Officer, welcomed the groups back to the general session. The leader of each group presented a set of prioritized questions, and clarifying questions were addressed. A general discussion of all the questions followed. The group noted the high degree of overlap among the questions. The group remarked on the potential biases involved with observational studies and the potential value of natural experiments.

Dr. Luce asked the patients for their impressions of the discussions and thoughts about research that should be performed. Comments included frustration with the lack of approved therapies for patients with progressive MS; frustration with lack of empowerment as a patient and the need for information, even if it is imperfect and based on observational studies; and the need for more patients' voices at meetings like this. There is also a need to translate existing information into communication models that patients can use. The role of new technology was also mentioned, such as measuring physical activity accurately over long periods of time as an outcome measure. Such data can be linked to electronic medical record data. It was remarked that, in addition to funding studies of CER, PCORI has programs to fund research communication and dissemination and training of patients.

VI. Next Steps

Drs. Selby and Bild thanked the workshop participants for their efforts before the meeting and engaging in discussions during the meeting and reminded them that the final questions would be sent by email the following day for prioritization and comment.

PCORI will review the discussions across all breakout groups, review the results of the prioritization, and discuss further internally and with the PCORI Science Oversight Committee.

VII. Appendix

Participants were sent a prioritization exercise via Survey Monkey, instructing them to prioritize their top six research questions. Each ranked question was assigned a point value with the highest ranked as 6, the lowest as 1. The non-ranked questions were given a zero.

There were 41 responses to the prioritization exercise.

Question	Score	Number of participants who ranked it at all	Number of participants who ranked it No. 1 or 2
J. What are the comparative benefits and harms of non-pharmacological and pharmacological approaches in relation to key symptoms (e.g., emotional health, fatigue, cognition, pain) in people with MS?	101	23	14
F. In people with progressive MS, what is the comparative effectiveness of different care delivery approaches (i.e., MS specialty center vs. community neurology; direct care vs. telemedicine; "specialized medical home" vs. community neurology delivery of care) in improving outcomes such as functional status, quality of life, symptoms, ER use, and hospitalization?	93	29	7
I. Does an integrative model of care along with DMT in a newly diagnosed individuals affect disability progression and symptoms (physical, emotional and cognitive) compared to treatment with DMT alone?	89	24	9
A: What are the comparative benefits and harms of different disease-modifying therapies in newly diagnosed relapsing, remitting multiple sclerosis on disease activity, disease progression, symptoms, and quality of life?	87	20	11
B. Among MS patients receiving a DMT who experience disease activity, what are the benefits and harms of continuing the same therapy versus changing to a new medication?	85	22	9
C. Is treatment escalation using DMTs as effective as starting treatment with higher efficacy treatments in early active, previously untreated patients?	65	19	5

E. What is the comparative effectiveness of stopping versus continuing therapy after a period of prolonged disease stability in patient with MS?	60	16	6
L. What are the benefits and harms of early vs. delayed treatment with DMTs, in terms of symptoms, function, QOL, and disease activity in treatment-naive patients recently-diagnosed patients (meeting McDonald criteria within 12 months)?	60	21	5
M. In patients who recently transitioned from relapsing to progressive MS or were recently diagnosed with SPMS, what are the benefits and harms of continuing compared to discontinuing DMTs on outcomes including but not limited to symptoms, QOL, function, disease activity, disability, and/or mortality?	59	17	7
H. In people with relapsing MS, what is the comparative effectiveness of physician-directed vs. allied health-directed vs. navigator-directed, vs. technological-enabled self-management tools for improving initial decision making, patient care experiences, decision regret, quality of life and adherence to therapy?	54	18	2
G. In people with relapsing MS within 2 years of diagnosis, what is the comparative effectiveness of changing DMT using a NEDA strategy (no relapse, no new MRI or enhancing lesion, no change in disability) vs. not changing DMT in terms of functional status, quality of life, symptoms, ER use, and hospitalization?	45	16	3
K. What are the comparative benefits and harms of specific dietary regimens in people with MS?	37	14	3
D. What is the comparative effectiveness of smoking cessation efforts upon disease activity, progression, symptoms, and quality of life in MS?	26	7	1
Total		**246**	**82**