



Cycle 3 2015 Funding Cycle

PCORI Funding Announcement: Treatment of Multiple Sclerosis

Published October 12, 2015

This PCORI Funding Announcement applies to the funding cycle that closes on February 16, 2015, at 5 p.m. (ET). Application guidelines, templates, and other resources are available at <http://www.pcori.org/2015-Cycle-3-Multiple-Sclerosis>.



About PCORI

The Patient-Centered Outcomes Research Institute (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 Congress in 2010 as a nonprofit, nongovernmental organization. PCORI's purpose, as defined by our authorizing legislation, 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."

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Overview

Published	October 12, 2015
Letter of Intent Due	November 12, by 5 p.m. (ET) Letters of Intent (LOIs) will be screened for responsiveness to this PCORI Funding Announcement (PFA) and fit to program goals. Only those applicants selected will be permitted to submit full applications. Notification of denial or approval to submit a full application will occur no later than December 18, 2015.
Summary	<p>The Patient-Centered Outcomes Research Institute (PCORI) seeks to fund randomized clinical trials (RCTs) or observational studies that compare two or more alternatives for the treatment of multiple sclerosis, with a focus on the effects of therapies on the symptoms experienced by patients with MS and on quality of life and functional status. Comparisons of the effects of disease-modifying therapies (DMTs) and DMT-based strategies, of non-DMT therapies aimed at specific symptoms, and of telerehabilitation versus conventional direct care, on functional status, fatigue, and quality of life are of interest.</p> <p>For this solicitation, PCORI is not requiring that relevant national patient organizations, professional organizations, and payer or purchaser organizations be formally included as partners and active participants prior to contract award. However, applicants should document that they have consulted with patients and other stakeholders to identify the important decisional dilemmas and evidence needs that will drive development of the research questions or reference previously documented decisional dilemmas. Successful applicants are required to work in collaboration with PCORI staff upon award of the proposed studies to establish a project Study Advisory Committee (SAC) (or other appropriate engagement body, see the Treatment of Multiple Sclerosis FAQs) that is comprised of national or regional organizations that represent, at a minimum, patients or families with lived experience, relevant clinicians, payers, and health plans. Other representation may be recommended in collaboration with PCORI, including individual patients with lived experience and other relevant stakeholders, among them scientific and methodological experts. The SAC serves to advise and assist the research team with further refinement of the study questions, outcomes, and protocol.</p> <p>PCORI expects most applications to propose study designs that use randomization, either of individual participants or clusters, to avoid bias due to confounding. However, we encourage investigators who identify exceptional opportunities, by virtue of natural experiments and the existence of large registries with sufficiently detailed data, to use observational designs to address the research questions. Note that this funding program does not support applications to conduct cost-effectiveness analysis, systematic reviews, or development or evaluations of shared decision-making or decision-support tools.</p> <p>PCORI strongly supports active engagement of patient and other stakeholders, and is committed to their meaningful participation in PCORI-funded research. All PCORI funding applicants are expected to consult with patients and other stakeholders on the decisional dilemma and evidence needs in preparation for the submission of LOIs and applications. Successful applicants will work in collaboration with PCORI staff upon award of the proposed studies to establish a project SAC that is comprised of national or regional representation of organizations that represent, at a minimum, patients or families with lived experience, relevant clinicians, payers, and health plans.</p>

Applicant Resources	See http://www.pcori.org/2015-Cycle-3-Multiple-Sclerosis
Key Dates	<p>Online System Opens: October 12, 2015</p> <p>Applicant Town Hall Session: October 22, 2015, 1 p.m. – 2:30 p.m. (ET)</p> <p>Letter of Intent (LOI) Deadline: November 12, 2015, by 5 p.m. (ET)</p> <p>Screening Notification: December 18, 2015</p> <p>Application Deadline: February 16, 2016, by 5 p.m. (ET)</p> <p>Merit Review Dates: May 2016</p> <p>Awards Announced: July 2016</p> <p>Earliest Project Start Date: September 2016</p>
Maximum Project Budget (Total Direct Costs)	<p>\$3-10 million per application, depending on research question</p> <p>Question 1 (DMTs): \$10M</p> <p>Question 2 (symptomatic treatments): \$3M</p> <p>Question 3 (telerehabilitation): \$5M</p>
Maximum Research Project Period	<p>Question 1 (DMTs): 5 years</p> <p>Question 2 (symptomatic treatments): 3 years</p> <p>Question 3 (telerehabilitation): 4 years</p>
Funds Available Up to	\$50 million
Eligibility	<p>Applications may be submitted by any private-sector research organization, including any nonprofit or for-profit organization; any public-sector research organization, including any university or college hospital or healthcare system, laboratory, or manufacturer; or unit of local, state, or federal government. All US applicant organizations must be recognized by the Internal Revenue Service. Nondomestic components of organizations based in the United States and foreign organizations may apply as long as there is demonstrable benefit to the US healthcare system and US efforts in the area of patient-centered research can be clearly shown. Organizations may submit multiple applications for funding. Individuals are not permitted to apply.</p>
Review Criteria	<ol style="list-style-type: none"> 1. Potential for the study to fill critical gaps and generate actionable evidence 2. Potential for the study findings to be adopted into clinical practice and improve delivery of care 3. Scientific merit (research design, analysis, and outcomes) 4. Patient-centeredness 5. Patient and stakeholder engagement
Contact Us	<p>Programmatic Inquiries: Contact the PCORI Helpdesk via email (sciencequestions@pcori.org), phone (202-627-1884), or complete the Research Inquiry Form (http://www.pcori.org/content/research-inquiry). PCORI will provide a response within three business days. However, we cannot guarantee that all questions will be addressed in a timely fashion when the inquiry is made three or fewer business days prior to an LOI or application deadline.</p> <p>Administrative, Financial, or Technical Inquiries: Contact the PCORI Helpdesk at pfa@pcori.org. PCORI will provide a response within two business days. Note that during the week of the application deadline, response times may exceed two business days. Applicants may also call the PCORI Helpdesk (202-627-1885). Applicants are asked to plan accordingly. It is the applicant's responsibility to submit the application on or before the application deadline.</p>
Other	Deadlines are at 5 p.m. (ET). If deadlines fall on a weekend or a federal holiday, the deadline will be the following Monday or the next day after the federal holiday.

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I. Introduction

Summary of Program

The Patient-Centered Outcomes Research Institute (PCORI) is launching this funding initiative to support patient-centered comparative clinical effectiveness research (CER) that addresses important questions about the treatment of multiple sclerosis (MS) with an emphasis on symptoms, quality of life, and functional status.

Competitive applications must address at least one of the three priority research questions described in this funding announcement. Additionally, applications should:

- Compare the effectiveness¹ of two or more alternatives for improving patient-centered outcomes
- Include patient populations representative of people with multiple sclerosis
- Propose projects that take place in typical clinical care and community settings
- Have a sufficiently large study population to enable precise estimates of effect sizes and to support evaluation of potential differences in intervention effectiveness in patient subgroups, such as type of MS and disease stage, gender, or racial and ethnic minority populations
- Have strong endorsement and study participation by relevant patient organizations, professional organizations, and payer or purchaser organizations

Background

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 difficulties, and other symptoms and complications. Approximately 400,000 Americans have MS. Most people with MS are diagnosed between 20 and 40 years of age, and there is a strong female predisposition.² The clinical course is highly variable, generally unfolding over decades, and symptoms and complications range from mild to the development of severe disability.

Multiple sclerosis is usually categorized into four groups based on the disease course: 1) relapsing-remitting (RRMS), accounting for 85 percent of new cases of MS; 2) secondary progressive (SPMS), which follows RRMS in 65 percent of cases; 3) primary progressive (PPMS), accounting for 10 percent of new cases; and 4) progressive relapsing (PRMS), the least common form or five percent of new cases.³

¹ Effectiveness is the extent to which an intervention does more good than harm in a broad mix of patients when provided under the usual circumstances of healthcare practice (modified from <http://ec.europa.eu/DocsRoom/documents/7581/attachments/1/translations/en/renditions/pdf>).

² Kamm, CP, Uitdehaag BM, Polman, CH. Multiple sclerosis: current knowledge and future outlook. *European neurology* 2014; 72:132-41.

³ Sadaka, Y, Verhey, LH, Shroff, MM, et al. 2010 McDonald criteria for diagnosing pediatric multiple sclerosis.

In RRMS, the patient experiences acute attacks (relapses), followed by full or partial recovery. It is estimated that 16–30 percent do not experience full recovery from their initial episode.⁴ Approximately half of patients experience some residual symptoms six months after an attack. Estimates of the annualized relapses rate among patients with RRMS range from 0.3–1.9, with an average of one per year.⁵

In approximately 20 percent of cases, the initial symptoms are blurred vision, poor contrast or color vision, or pain on eye movement caused by optic neuritis.⁶ Fatigue is more common in people with MS than in the general population, affecting 33–75 percent of people with MS.⁷ Other common symptoms include numbness or tingling, spasticity, bladder problems, pain, cognitive changes, and depression. A more complete list of symptoms and treatments is included in the following discussion. About 10 percent of MS patients are unable to walk 10 years after the initial diagnosis.⁸

The evolution of RRMS to SPMS is highly variable,⁹ but the median time for those who progress from RRMS to SPMS has recently been reported as 19 years.⁶ Older age, male sex, presentation with spinal-cord-related symptoms (such as motor control or urinary control), incomplete remissions, short remission period between the first two attacks, and increased number of attacks in the first two to five years of onset are associated with a faster progression to a secondary progressive course.¹⁰

The progressive forms of the disease (PPMS and SPMS) are characterized by a steady deterioration in neurologic function over a six-month period, associated with new symptoms and signs.⁴ Primary progressive MS shows progression from the time of disease onset, whereas SPMS shows progression after initial presentation as RRMS. Progressive relapsing MS, the least common form, is associated with both acute relapses and continuing progression between relapses from the time of onset.

The goals of treatment for MS can be characterized as treatment of acute relapses (generally with corticosteroids), disease-modifying therapy (DMT, focused on altering the natural history of MS), and treatment of symptoms.⁶ There are many sets of clinical guidelines available that do not always agree,¹¹ and a recent systematic review of direct comparisons of even the oldest and most commonly used

Annals of Neurology 2012; 72:211–23.

⁴ Confavreux, C, Vukusic, S. The clinical course of multiple sclerosis. *Handbook of clinical neurology* 2014; 122:343–69.

⁵ Inusah, S, Sormani, MP, Cofield, SS, et al. Assessing changes in relapse rates in multiple sclerosis. *Multiple sclerosis* (Houndmills, Basingstoke, England) 2010; 16:1414–21.

⁶ Kamm, CP, Uitdehaag, BM, Polman, CH. Multiple sclerosis: current knowledge and future outlook. *European neurology* 2014; 72:132–41.

⁷ Berger, JR, Pocoski, J, Preblick, R, Boklage, S. Fatigue heralding multiple sclerosis. *Multiple sclerosis* (Houndmills, Basingstoke, England) 2013; 19:1526–32.

⁸ Multiple Sclerosis: Natural History and Disease Courses. (n.d.). Retrieved May 8, 2015, from <http://www.healthline.com/health/multiple-sclerosis/multiple-sclerosis-disease-courses/>.

⁹ Kantarci, OH, Weinshenker, BG. Natural history of multiple sclerosis. *Neurologic Clinics* 2005; 23:17–38.

¹⁰ Harvey, S. (2013, September 18). *Multiple sclerosis*. University of Maryland Medical Center. Retrieved May 5, 2015, from <http://umm.edu/health/medical/reports/articles/multiple-sclerosis/>.

¹¹ Trisolini, M. (2008, December 8). National Guideline Clearinghouse | Expert Commentaries: Comparison of Multiple Sclerosis Guidelines Underscores Need for Collaboration. Retrieved May 7, 2015, from <http://www.guideline.gov/expert/expert-commentary.aspx?id=16443/>.

medications found insufficient evidence to draw conclusions about effects on patient-reported outcomes, such as quality of life.¹²

The number of DMTs has increased dramatically since the mid-1990s. There are currently 12 such DMTs approved by the Food and Drug Administration (FDA) for use in patients who are experiencing relapses, mainly RRMS and PRMS.¹³ There is very little information about differences in the effectiveness of these agents or of various sequences or combinations of DMTs on the major symptoms of MS. There are currently no FDA-approved therapies for PPMS and SPMS, unless the patient continues to experience relapses. Most important, there are few head-to-head comparison studies of DMTs for either the initial treatment of RRMS or of follow-on treatments in patients for whom initial DMT treatment has failed, including strategies for sequencing or combining agents, changing to a different DMT, or escalating DMT dose.¹⁴

Research Topic Prioritization and Strategy

PCORI relies on input from multiple stakeholders to set its research priorities. Members of its advisory panels include patients, clinicians, researchers, purchasers, payers, industry, and other healthcare stakeholders. Many stakeholders have asked PCORI to consider funding research on multiple sclerosis. In January 2014, PCORI's Advisory Panel on Assessment of Prevention, Diagnosis, and Treatment Options ranked MS as a high-priority topic. PCORI then convened a series of multi-stakeholder workshops between October 2014 and April 2015 to obtain more specific input on whether comparative effectiveness research (CER) questions existed that could be addressed by PCORI-funded research. More than 40 invited stakeholders attended the final and largest [workshop](#)¹⁵ in person, on April 2, 2015. The meeting was open to the public via teleconference and webinar.

Before the April workshop, PCORI asked invited participants to propose specific CER questions about the treatment of MS. PCORI staff grouped the submitted questions into four categories: Comparison of DMTs, including differential effects in subgroups; Care strategies; Nonpharmacologic and non-DMT therapy for specific symptoms and overall health; and Timing of therapy and study design. These questions were discussed, revised, and ranked by the participants during breakout sessions at the workshop. PCORI staff used the results of these rankings to inform its selection of high-priority research questions and approaches.

The research questions for this funding announcement were reviewed and approved by PCORI's Board of Governors (Board) on September 28, 2015.

Priority Research Questions

Applications must propose RCTs and observational studies that address one of the following priority

¹² La Mantia, L, Di Pietrantonj, C, Rovaris, M, et al. Interferons-beta versus glatiramer acetate for relapsing-remitting multiple sclerosis. The Cochrane database of systematic reviews 2014;7:CD009333.

¹³ Medications. (n.d.). Retrieved May 7, 2015, from <http://www.nationalmssociety.org/Treating-MS/Medications/>.

¹⁴ Canadian Agency for Drugs and Technologies in Health. Comparative clinical and cost-effectiveness of drug therapies for relapsing-remitting multiple sclerosis [Internet]. Ottawa: The Agency; 2013 Oct. (*CADTH Therapeutic Review* vol.1, no. 2b).

¹⁵ Available at <http://www.pcori.org/events/2015/prioritizing-comparative-effectiveness-research-questions-treatment-multiple-sclerosis>.

research questions. Applicants should explain the relevance of comparisons proposed in the application, citing evidence gaps that are justified on the basis of up-to-date literature reviews, and the potential of the proposed study to fill the evidence gap and lead to changes in practice and better patient-centered outcomes. Given the heterogeneity in clinical presentation and in the course of multiple sclerosis, applicants must carefully consider how the results of their proposed study will be applied to important subgroups. PCORI is particularly interested in studies in populations with important health disparities.

The three priority research questions that PCORI has identified in the treatment of MS are:

1. What are the comparative benefits and harms of different DMTs or therapeutic strategies in patients with relapsing, remitting multiple sclerosis on symptoms, functioning, quality of life, disease activity, and disease progression? Strategies may include comparisons of initial DMT treatment or comparisons of follow-on treatments in patients for whom initial DMT treatment has failed, including strategies for sequencing or combining agents, changing to a different DMT, or escalating DMT dose.
2. What are the comparative benefits and harms of different approaches, other than DMTs, for ameliorating important symptoms in people with MS? Symptoms of interest include fatigue, difficulty walking, memory or attention problems (cognition), bladder problems, numbness or tingling, and pain. Studies of patients with progressive forms of MS are of particular interest.
3. What is the comparative effectiveness of telerehabilitation versus conventional direct care interventions for improving outcomes in people with MS, such as functional status, fatigue, and quality of life?
 - Studies should evaluate the effectiveness of telerehabilitation interventions to enhance community-based primary care or neurology practice for patients who do not have access to specialty centers. Applications that employ intervention(s) already in practice are especially attractive.
 - Studies should examine the impact of the telerehabilitation strategies in various subpopulations, including individuals with low socioeconomic status and patients with progressive disease.

PCORI seeks to fund studies that address each of the three priority questions but does not commit to such. PCORI will consider the merit of each application and its responsiveness to the relevant priority question as well as programmatic requirements and portfolio balance when making final funding recommendations.

More information about each of the research questions follows.

Question 1. What are the comparative benefits and harms of different DMTs or therapeutic strategies in patients with relapsing, remitting multiple sclerosis on symptoms, functioning, quality of life, disease activity, and disease progression? Strategies may include:

- Comparisons of initial DMT treatment

- Comparisons of follow-on treatments in patients for whom initial DMT treatment has failed, including strategies for sequencing or combining agents, changing to a different DMT, or escalating DMT dose. Note that patients with clinically isolated syndrome may be included with appropriate justification in a study of initial DMT treatment

There are now 12 FDA approved disease-modifying therapies to treat MS,¹⁶ including three oral therapies that have been introduced since 2010.¹⁷ There is a lack of consensus about what constitutes best initial therapy,^{20,18} and there is currently no Class I evidence supporting the choice of a second-line therapy.¹⁹ The last set of guidelines from the American Academy of Neurology regarding use of DMTs in MS is from 2002,²⁰ when most of the current DMTs were not yet available.

The most recent guidelines from the Canadian Agency for Drugs and Technologies in Health (CADTH) state that there is a limited number of RCTs directly comparing treatments for RRMS.²¹ The CADTH identifies the following research gaps:

- Evidence for sequencing of therapy, specifically clinical trials comparing treatment strategies in patients with RRMS in whom treatment has failed or who are unable to tolerate initial therapy
- Clinical trials that specifically compare treatment strategies of “add-on” to “switch” therapies
- Evaluation of disease outcomes in patients stopping therapy after a prolonged course

The report also notes the lack of clinical trials that capture outcomes of particular interest to patients, including fatigue, walking ability, cognitive function, and quality of life.

Given the lack of head-to-head studies of different DMTs to treat RRMS, PCORI would like to support such comparative studies, including for initial DMT treatment and for patients for whom initial DMT treatment has failed. Ideally, these would be RCTs that compare two or more such medications and include appropriate patient-centered outcomes.

In addition to lack of comparative data on many DMTs for initial therapy, people with multiple sclerosis and their care providers also face uncertainty about modifying DMT once started. This situation is commonly faced by patients, because they experience a relapse while on medication or become

¹⁶ Medications. (n.d.). Retrieved May 7, 2015, from <http://www.nationalmssociety.org/Treating-MS/Medications/>.

¹⁷ Sturm, D, Gurevitz, SL, Turner, A. Multiple sclerosis: a review of the disease and treatment options. *The Consultant pharmacist*, the journal of the American Society of Consultant Pharmacists 2014; 29:469–79.

¹⁸ Harrison, DM. Multiple sclerosis. *Annals of internal medicine* 2014; 160:ITC4-2-ITC4-18; quiz ITC4-6.

¹⁹ Yamout, B. Diagnosis and treatment of multiple sclerosis: MENACTRIMS consensus guidelines. *Multiple sclerosis and related disorders* 2014; 3:766.

²⁰ Goodin, DS, Frohman, EM, Garmany, GP, Jr., et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology* 2002; 58:169-78.

²¹ Management of Relapsing-Remitting Multiple Sclerosis. Ottawa, ON: CADTH March 2013.

unwilling to tolerate the side effects or risks associated with a DMT. A recent systematic review identified 16 relevant studies that included complete information about the long-term benefits and harms surrounding the discontinuation of DMT and concluded that there is little information available to guide decisions to discontinue DMT.²² Thus, studies of treatment algorithms that guide selection of therapies may also be appropriate and important comparators.

Outcome Measures

One well-acknowledged barrier to determining the effects of treatments in MS is the lack of scales to assess disability,²³ which has led to the creation of a public-private partnership between FDA, the European Medicines Agency, and industry to create sensitive, clinically meaningful, and reliable outcome measures to use in clinical trials of MS.²⁴ In early deliberations of this group, it was noted that outcomes other than disability are also important to patients, including pain, fatigue, and bladder dysfunction, and impacts on cognitive function.

The most widely used scale to measure disability in studies of multiple sclerosis is the Expanded Disability Status Scale (EDSS). While there are criticisms about feasibility of its use and scale and distribution properties,²⁵ investigators need not be confined to its use and should propose to include the best available measures – meaningful, valid, and feasible to measure – to assess outcomes relevant for the proposed research question and study design. Consensus guidelines should be considered in designing studies,²⁶ but investigators must assure that outcomes are patient-centered, correlate with accepted clinical outcome measures, and adhere to PCORI’s Methodology Standards.²⁷ It is strongly encouraged that measures include well-established measures such as the EDSS and the MS Functional Composite.²⁸

The participants of the PCORI multi-stakeholder workshop in April 2015 proposed similar questions, noting the lack of evidence available to guide decisions about escalating, discontinuing, or changing DMTs and about the timing of initial therapy. Studies of treatment algorithms that guide selection of therapies and changes in therapies are also appropriate comparators.

²² 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/.

²³ Guideline on clinical investigation of medicinal products 5 for the treatment of Multiple Sclerosis. (2015, February 26). Retrieved May 13, 2015, from

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/10/WC500133438.pdf

²⁴ Rudick, RA, Larocca, N, Hudson, LD. Multiple Sclerosis Outcome Assessments Consortium: Genesis and initial project plan. *Multiple sclerosis* (Houndmills, Basingstoke, England) 2014; 20:12–7.

²⁵ Meyer-Moock, S, Feng, YS, Maeurer, M, Dippel, FW, Kohlmann, T. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. *BMC neurology* 2014; 14:58.

²⁶ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500185161.pdf.

²⁷ <http://www.pcori.org/assets/2013/11/PCORI-Methodology-Report.pdf/>.

²⁸ Fischer, JS, Rudick, RA, Cutter, GR, Reingold, SC. The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force. *Multiple sclerosis* 1999; 5:244–50.

Question 2. What are the comparative benefits and harms of different approaches, other than DMTs, for ameliorating important symptoms in people with MS? Symptoms of interest include fatigue, difficulty walking, memory or attention problems (cognition), bladder problems, numbness or tingling, and pain. Studies of patients with progressive forms of MS are of particular interest.

This topic was the top-ranked issue from the PCORI multi-stakeholder meeting. People with multiple sclerosis face a myriad of symptoms and complications over the course of their illness, and there is a range of treatment options for each condition. More common symptoms include fatigue; walking difficulties; numbness or tingling; spasticity; weakness; vision problems; dizziness or vertigo; bladder problems; sexual problems; bowel problems; pain; cognitive changes; emotional changes; and depression. Less common symptoms include speech problems; swallowing problems; tremor; seizures; breathing problems; itching; headache; and hearing loss. A wide range of both pharmacological and nonpharmacological approaches are available, as noted below:

Symptom	Commonly Used Treatment Options
Fatigue	Pharmacologic: Amantadine, methylphenidate, SSRIs, aspirin, modafinil, dextroamphetamine salts, lisdexamfetamine Nonpharmacologic: Multidisciplinary rehabilitation programs, physical therapy, exercise training, yoga
Walking difficulties	Pharmacologic: Dalfampridine Nonpharmacologic: Physical therapy
Numbness or tingling	Pharmacologic: No medications have been proven effective for numbness. For tingling, gabapentin, pregabalin, carbamazepine, oxcarbazepine, duloxetine, tricyclic antidepressants, lidoderm patches, capsaicin cream
Spasticity	Pharmacologic: Baclofen, tizanidine, dantrolene, clonazepam, gabapentin, levetiracetam, clonidine, intrathecal baclofen. Nonpharmacologic: Botulinum toxin, physical therapy, exercise, transcranial magnetic stimulation, electromagnetic therapy, Transcutaneous electrical nerve stimulation (TENS), cannabinoids
Muscle weakness	Pharmacologic: dalfampridine Nonpharmacologic: Exercise, assistive devices, medication, physical therapy, occupational therapy, Pilates training
Vision problems	Pharmacologic: Corticosteroids (for optic neuritis) Nonpharmacologic: Eye rest, special prisms
Dizziness or vertigo	Pharmacologic: Motion-sickness or anti-nausea drugs (e.g., meclizine, scopolamine, ondansetron), diazepam, valium (benzodiazepines) Nonpharmacologic- vestibular therapy

Symptom	Commonly Used Treatment Options
Bladder problems	Pharmacologic: Onobotulinumtoxin A, desmopressin, tolterodine, oxybutynin, darifenacin, tamsulosin, terazosin, prazosin, propantheline, trospium chloride, imipramine, solifenacine succinate, capsaicin Nonpharmacologic: Intermittent catheterization, physical therapy, pelvic floor training, bladder stimulators
Sexual problems	Pharmacologic: Pro-erectile medications for men Nonpharmacologic: Vaginal lubricants for women
Bowel problems	Nonpharmacologic: Dietary and lifestyle approaches, enemas, suppositories, laxatives for constipation
Pain	Pharmacologic: Gabapentin, pregabalin, carbamazepine, oxcarbamazepine, duloxetine, tricyclic antidepressants, lidoderm patches, capsaicin cream Nonpharmacologic: Cannabinoids, marijuana, massage therapy, acupuncture
Cognitive changes	Pharmacologic: Interferon, donepezil, galantamine, modafinil, amphetamines Nonpharmacologic: Multidisciplinary rehabilitation programs, exercise training, behavioral training
Emotional changes	Nonpharmacologic: Physical therapy, exercise training, yoga, mindfulness-based interventions
Depression	Pharmacologic: Pharmacologic management as evaluated in non-MS populations Nonpharmacologic: Psychotherapy, yoga, exercise training, acupuncture

Source: PCORI Topic Brief. (<http://www.pcori.org/sites/default/files/PCORI-Prioritizing-CER-Questions-Treatment-of-MS-Workshop-Topic-Brief-040215.pdf>)

There are at least 10 sets of treatment guidelines, which do not all agree²⁹ and tend to focus on relatively narrow clinical issues, such as use of immunizations in people with MS. A recent review of treatment recommendations for treatment of symptoms of MS found many areas with low levels of evidence.³⁰ There are also very few head-to-head comparisons of treatments for common symptoms listed in ClinicalTrials.gov.

PCORI is interested in receiving applications that propose to compare two or more treatment options for specific symptoms in people with MS where uncertainty exists. Applicants should justify the choice of

²⁹ Trisolini, M. (2008, December 8). National Guideline Clearinghouse | Expert Commentaries: Comparison of Multiple Sclerosis Guidelines Underscores Need for Collaboration. Retrieved May 7, 2015, from <http://www.guideline.gov/expert/expert-commentary.aspx?id=16443/>.

³⁰ Multiple Sclerosis: Management of Multiple Sclerosis in Primary and Secondary Care. London: National Clinical Guideline Centre, 2014.

symptom and compared strategies by documenting both the importance of the symptom to patients and the important decisional dilemma that patients, caregivers, clinicians, and other stakeholders face.

As discussed under Question 1, applicants should propose to include the best available measures – meaningful, valid, and feasible to measure – to assess outcomes relevant for the proposed research question and study design. Consensus guidelines should be considered in designing studies, but investigators must assure that outcomes are patient-centered, correlate with accepted clinical outcome measures, and adhere to PCORI’s Methodology Standards.

Question 3. What is the comparative effectiveness of telerehabilitation versus conventional direct care interventions for improving outcomes in people with MS, such as functional status, fatigue, and quality of life?

- Studies should evaluate the effectiveness of telerehabilitation interventions to enhance community-based primary care or neurology practice for patients who do not have access to specialty centers. Applications that employ intervention(s) already in practice are especially attractive.
- Studies should examine the impact of the telerehabilitation strategies in various subpopulations, including individuals with low socioeconomic status and patients with progressive disease.

Multiple sclerosis is a chronic condition of the central nervous system with heterogeneous clinical manifestation. Thus, the care of patients with MS requires a multidisciplinary approach and a comprehensive strategy for symptom management, function improvement, disease course modification, relapse prevention, and relapse management. Common symptoms such as muscle weakness, fatigue, coordinative and motor impairments, and depression can lead to reduced mobility and overall functional status. Balance and postural control (PC) disorders are among the most frequent motor disorder symptoms associated with MS, as these symptoms are present in 20 percent of patients with MS at onset and chronic in 80 percent of cases.³¹ Balance and PC disorders in patients with MS are associated with difficulty standing and performing functional activities, thereby significantly affecting quality of life.³²

Neurorehabilitation programs are among the most popular therapies aimed at reducing the disabilities and social disadvantages that result from MS, but these resources are limited and deficient in the clinical setting because of the time-constrained nature of rehabilitation. Furthermore, poor adherence to rehabilitation, limited patient education, and access to specialized care can be barriers to treatment.³³ In response to this situation, interest has recently increased with regard to the development of eHealth projects. In the context of eHealth, telerehabilitation (TR) is the delivery of rehabilitation services via

³¹ Cattaneo, D.; Jonsdottir, J. Sensory impairments in quiet standing in subjects with multiple sclerosis. *Mult. Scler.* 2009, 15, 59–67.

³² Matsuda, P.N.; Shumway-Cook, A.; Bamer, A.M.; Johnson, S.L.; Amtmann, D.; Kraft G.H., Falls in multiple sclerosis. *PM&R* 2011, 3, 624–632.

³³ Petajan, JH, White, AT. Recommendations for physical activity in patients with multiple sclerosis. *Sports Med.* 1999; 27(3): 179–91.

electronic systems using information and communication technologies (ICT).³⁴ TR has been rapidly developing over the last decade and is now moving from single-case, or small sample research, to controlled trials with larger samples, making it primed for comparative effectiveness research.^{35,36}

Prior evaluations have demonstrated success of various telerehabilitation interventions at improving outcomes for patients with MS:

- Finkelstein et al. (2008) found that a home-based physical telerehabilitation can improve functional outcomes in patients with MS. The participants of the study also demonstrated a very high level of support for the home-based physical telerehabilitation program.³⁷
- Frevel et al. (2015) found that an Internet-based home training program had positive impacts on improving balance in patients with MS. The results of the study show that the utilized e-Training program compared to established and qualified training methods, such as hippotherapy, especially improved balance and walking ability.³⁸
- Ortiz-Gutiérrez (2013) reported positive outcomes in balance and postural control among patients with multiple sclerosis who completed a virtual-reality-system telerehabilitation program.³⁹
- Finlayson et al. (2011) reported a significant reduction in fatigue among patients with MS who completed a group-based, teleconference-delivered fatigue management program, compared to a wait-list control group.⁴⁰

Despite the demonstrated success of various telerehabilitation interventions at improving outcomes for patients with MS and the growing number of studies evaluating various interventions of telerehabilitation for persons with MS, the evidence base for their effectiveness has important gaps. There is insufficient evidence to indicate what types of telerehabilitation interventions are most effective and in which community-based practice settings. The quality of the evidence is further limited by studies with small samples that are underpowered to examine the heterogeneity of effect (HTE) for different groups of patients with MS, including those who are geographically remote or lower socio-economic status and who have progressive disease. Recent systematic reviews call for more robust trials

³⁴ Cano-de la Cuerda, R.; Muñoz-Hellín, E.; Alguacil-Diego, I.M.; Molina-Rueda, F. Telerehabilitation and neurology. *Rev. Neurol.* 2010, 51, 49–56.

³⁵ Winters, JM. Telerehabilitation research: Emerging opportunities. *Annu Rev Biomed Eng.* 2002; 4:287–320.

³⁶ Russell, TG. Physical rehabilitation using telemedicine. *J Telemed Telecare.* 2007; 13(5):217–20.

³⁷ Finkelstein, J., Lapshin, O., Castro, H, Cha, E., Provance, P. (2008). Home-based physical telerehabilitation in patients with multiple sclerosis: A pilot study. *Journal of Rehabilitation Research & Development.* 45(9): 1361-1374.

³⁸ Frevel, D., Maurer, M. (2015). Internet-based home training is capable to improve balance in multiple sclerosis: a randomized controlled trial. *European Journal of Physical and Rehabilitation Medicine.* 51: 23–30.

³⁹ Ortiz-Gutiérrez, R., Cano-de-la-Cuerda, R., Galán-del-Río, F., Alguacil-Diego, I., Palacios-Ceña, D., Miangolarra-Page, J. (2013). A Telerehabilitation Program Improves Postural Control in Multiple Sclerosis Patients: A Spanish Preliminary Study. *International Journal of Environmental Research and Public Health.* 10: 5697–5710.

⁴⁰ Finlayson, M., Preissner, K., Cho, C., Plow, M. (2011). Randomized trial of a tele-conference-delivered fatigue management program for people with multiple sclerosis. *Mult.Scler.* 17: 1130–1140.

to build the evidence base for the clinical effectiveness of these interventions.^{41,42}

In response, PCORI seeks to fund studies that compare telerehabilitation models of care to conventional direct care for patients with MS. Outcomes of interest include, but are not limited to, functional status, fatigue, and quality of life. PCORI is especially interested in funding studies with sufficient power to detect HTE for various MS populations, including individuals without access to specialty centers being managed by community-based primary-care physicians or neurologists, those with progressive disease, and those of low socio-economic status. PCORI is not interested in proposals to study the efficacy of a new model of telerehabilitation; acceptable models must have established efficacy or effectiveness. Telerehabilitation approaches available in practice are especially encouraged. Applicants must describe the intervention goals, number and extent of active components (e.g., physical activity, educational, or behavioral training components), duration and intensity, and mode of delivery. Conventional direct-care comparators must be fully described and include accurately measured components of the rehabilitation programs delivered to persons with MS who live in communities without access to specialty centers.

Responses to this question should include plans to describe clearly the components and integration of services that comprise the care systems being compared. PCORI discourages proposals to study the efficacy of a new model of care or comparisons of a model of care to undefined “usual care” (or no specific intervention). Rather, studies should compare well-defined conventional direct care (clinical and programmatic components must be specified) to telerehabilitation intervention(s) that enhance community-based primary care or neurology practice for patients who do not have access to specialty centers. Studies must measure and report details of the content of care that individual patients receive to enable both replication of findings and analyses to determine relationships between specific components of the care intervention and outcomes. Studies should have follow-up of individual patients appropriate for the research question. For example, studies of symptom amelioration may require 12 months, whereas studies of DMT strategies may require three years of follow-up.

Study Design Considerations

Observational studies are most appropriate when randomization is not feasible and when rich, population-based clinical data can be obtained in whole or in part from existing databases or can be collected prospectively. Applicants must carefully address how they will control for confounding that is inherent in observational studies. One important and particularly relevant form of confounding for the treatment of MS is that patient characteristics or patient or clinician preferences may lead to the prescription or recommendation of a specific treatment. These characteristics or preferences may also be related to medication adherence and to important outcomes and therefore confound the relationship between the treatment and the outcome. In addition, estimates of differences in effectiveness between two active interventions or therapies (i.e., comparative effectiveness) may be relatively small, but nevertheless important—if real. The threat that selection bias or confounding may explain modest differences in observational studies is great. Therefore, applicants proposing

⁴¹ Khan, F, Amatya, B, Kesselring, J, Galea, M. Telerehabilitation for persons with multiple sclerosis. *Cochrane Database of Systematic Reviews* 2015, Issue 4.

⁴² Amatya, B, Galea, M, Kesselring, J, Khan, F. (2015). Effectiveness of telerehabilitation interventions in persons with multiple sclerosis: A systematic review. *Mult Scler Relat Disord.* 4(4): 358–69.

observational studies should carefully explain how such bias will be evaluated and minimized in the study design.

As a condition, MS poses unique challenges for identifying which treatments work best for which people because of its variable presentation and clinical course, wide range of symptoms and outcomes, and lack of evidence for how to tailor treatment choices, particularly for the DMTs. Also, given these complexities, as well as changes in therapies experienced by patients on the basis of symptoms and periodic measures of disease progression, proposals to use observational methods should strongly consider the use of innovative observational methods such as dynamic marginal structural modeling⁴³ and machine learning.^{44,45}

Randomized clinical trials should be on the pragmatic end of the explanatory-pragmatic spectrum.⁴⁶ These should be designed to maximize applicability of the study's results in routine clinical practice. Adaptive trials⁴⁷ or the platform trial model⁴⁸ that can accommodate the appearance of new treatments or changes in treatments during the course of the study are particularly encouraged for RCTs.

Large differences in presentation, symptoms, and disease course among people with MS, as well as factors that are associated with different prognoses, such as gender and race and ethnicity or other factors, such as biomarkers,⁴⁹ require that RCTs be designed to enable important subgroups to be examined. Thus, sample sizes must be sufficient to enable differences to be found in comparative effectiveness between different patient subgroups and to be able to identify HTE across important subgroups.

Funds Available

PCORI will devote up to \$50 million in total costs under this PCORI Funding Announcement (PFA). Please see Budget and Project Duration section for details.

For each priority question, it is expected that project budgets and duration will vary substantially, depending on the topic and approach selected, needs for recruitment and primary data collection, length of follow-up, and analytic complexity. PCORI seeks efficient studies, such as those that take advantage of large populations already under observation, and the supportive involvement of delivery systems or health plans to enhance recruitment and data collection. Treatment-related costs should be

⁴³ Neugebauer, R, Fireman, B, Roy, JA, O'Connor, PJ, Selby, JV. Dynamic marginal structural modeling to evaluate the comparative effectiveness of more or less aggressive treatment intensification strategies in adults with type 2 diabetes. *Pharmacoepidemiology and drug safety* 2012;21 Suppl 2:99–113.

⁴⁴ Van der Laan, MJ, Polley, EC, Hubbard, AE. Super learner. *Statistical applications in genetics and molecular biology* 2007;6: Article25.

⁴⁵ Hubbard, A, Munoz, ID, Decker, A, et al. Time-dependent prediction and evaluation of variable importance using superlearning in high-dimensional clinical data. *J Trauma Acute Care Surg* 2013; 75:S53–60.

⁴⁶ Loudon, K, Treweek, S, Sullivan, F, Donnan, P, Thorpe, KE, Zwarenstein, M. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ (Clinical research ed)* 2015; 350:h2147.

⁴⁷ Luce, BR, Kramer, JM, Goodman, SN, et al. Rethinking randomized clinical trials for comparative effectiveness research: the need for transformational change. *Annals of internal medicine* 2009;151:206–9.

⁴⁸ Berry, SM, Connor, JT, Lewis, RJ. The platform trial: an efficient strategy for evaluating multiple treatments. *JAMA* 2015; 313:1619–20.

⁴⁹ Harris, VK, Sadiq, SA. Biomarkers of therapeutic response in multiple sclerosis: current status. *Molecular Diagnosis & Therapy* 2014; 18:605–17.

covered as part of normal clinical care. Funding requests to develop or build on initial collaboration between researchers and patient and stakeholder groups are also not appropriate for this funding announcement.

II. Guidance for Preparing Applications

Specific Requirements

The proposed study should meet all of the following requirements:

- Focus on a comparative effectiveness question that is important to patients and other decision makers
- Demonstrate consultation with patients and other stakeholders, or their representative groups, or reference previously documented decisional dilemmas, in order to determine whether the study is answering a critical question—one that, if adequately answered, would substantially improve decision making
- Propose a sample size that is sufficiently large to allow for precise estimation of hypothesized effect sizes or for clear demonstration of noninferiority; in addition, the sample size must support testing of a priori hypotheses related to potential differences in effectiveness in relevant patient subgroups (HTE)
- Examine diverse populations receiving care in real-world settings
- Document strong interest from and support by host delivery systems and clinical care settings
- Have strong interest from and support by host delivery systems and clinical care settings
- Specify broad and simple eligibility criteria that will allow wide generalization of results, while attending appropriately to any ethical concerns of excess risk in some patient subgroups
- Compare interventions that are known to be efficacious, effective, or commonly in use, and can be implemented in real-world settings
- Include patient-reported outcomes as a primary outcome, when appropriate
- Provide preliminary evidence of the potential for efficient recruitment, high participation rates, and appropriate oversight by local or centralized Institutional Review Boards (IRBs), including plans for streamlining or waiving individual informed consent in cases of low-risk interventions. PCORI believes that the intensity of oversight and the complexity of informed consent procedures should be closely related to the degree of risk from study participation. Applicants must address this issue and should present evidence that the study will not encounter significant barriers to recruitment or participation

- Adhere to all applicable [PCORI Methodology Standards](#)⁵⁰
- In the case of randomized trials, also adhere to current best practices (standardized inclusion and exclusion criteria; proper randomization; techniques to minimize potential for missing data; appropriate safety monitoring, including establishment of a data and safety monitoring board [DSMB] or indication of why such a board is unnecessary)
- Include a plan for sharing de-identified data for access by other researchers following completion of the study

To carry out pragmatic studies, facilitate adoption of findings in a real-world setting, and maximize the efficient use of resources, care must be taken to prevent trials from becoming more complex and onerous than necessary. The applicant is encouraged to be creative and consider innovative strategies such as the following, as appropriate and feasible:

- Consult with patients and other stakeholders on their decisional dilemma and evidence needs **or reference previously documented decisional dilemmas** in preparation for the submission of Letters of Intent (LOIs) and the full applications
- Carefully describe the pertinent evidence gaps and why the project questions represent decisional dilemmas for patients, caregivers and families, and other stakeholders, including clinicians and policy makers. Similarly, applicants should document why project outcomes are especially relevant to patients and meaningful endpoints for patients and their families and also minimize disruption to participants' daily routines (e.g., minimize participant visits intended solely for study-assessment purposes; capture PROs during office visits, electronically or via phone)
- Design the study so that the conduct can be integrated with routine clinic or office operations as seamlessly as possible
- Use efficient methods to obtain participant consent while still meeting ethical and legal requirements
- Capitalize on the existing electronic health records and other computerized information to identify and recruit eligible patients, monitor study conduct and patient safety, and collect study outcomes information. Specifically, PCORI encourages proposals that utilize the infrastructure of the National Patient-Centered Clinical Research Network (PCORNet)
- If data standardization and interoperability across study sites have not already been accomplished, develop methods that will enhance the standardization of data that are accessed from different electronic health record systems

Nonresponsiveness

Applications will be considered nonresponsive to this PFA if the proposed research:

- Tests efficacy within a tightly-protocol-controlled research setting, as opposed to more real-

⁵⁰ Available at <http://www.pcori.org/research-results/research-methodology/>.

world, pragmatic CER

- Conducts a formal cost-effectiveness analysis
- Directly compares the costs of care between two or more alternative approaches to providing care
- Primarily focuses on the natural history of disease or proposes instrument (for data collection) development, pharmacodynamics, and fundamental science or study of biological mechanisms
- Evaluates new or existing decision support tools; this includes the development and evaluation of a decision support or shared decision tool or system for patients, clinicians, or both patients and clinicians
- Develops clinical prediction or prognostication tools

Proposals that include studies of these issues may measure and report utilization of any or all health services, but may not employ direct measurements of costs of care. For further information, please reference our [cost-effectiveness analysis FAQs](#).

PCORI does have an interest, however, in studies that address questions about conditions that lead to high costs to the individual or to society. This is included in our review criterion on impact of the condition on the health of individuals and populations. Thus, PCORI is interested in studies that:

- Examine the effect of costs on patients, such as patients' out-of-pocket costs, hardship, or lost opportunity, or costs as a determinant of or barrier to access to care
- Address cost-related issues, such as the resources needed to replicate or disseminate a successful intervention
- Evaluate interventions to reduce health system waste or increase health system efficiency

Addressing this issue specifically, our funding announcements say that "proposals that include studies of these issues without utilizing a formal cost-effectiveness analysis or directly measuring and comparing costs of care alternatives will be considered responsive and will be reviewed."

Features of Patient-Centered Outcomes Research (PCOR)

PCOR helps patients and their caregivers communicate and make informed healthcare decisions, allowing their voices to be heard in assessing the value of healthcare options. This research:

- Assesses the benefits and harms of preventive, diagnostic, therapeutic, or palliative care to inform decision making, highlighting the choices that matter to people
- Is inclusive of an individual's preferences, autonomy, and needs, focusing on outcomes that people notice and care about, such as survival, functioning, symptoms, and health-related quality of life
- Incorporates a wide variety of settings and diversity of participants to address individual differences and barriers to implementation and dissemination

- Directly compares clinical interventions that are currently available or in general use in the clinical settings
- Obtains the perspectives of stakeholders to address the burdens to individuals, access to care, quality of care, and requirements for technology and personnel

Leveraging Existing Resources

Investigators are encouraged to propose studies that leverage existing resources, such as adding PCOR to an existing large clinical trial or analyzing existing large databases that contain valuable, relevant information that may be used to answer important CER questions.

PCORI strongly encourages researchers and stakeholder groups to collaborate and combine data and efforts, such as registries, patient networks, and existing studies and, as appropriate, to form collaborations that will enable the study of sufficiently large and heterogeneous groups of people with MS.

Preliminary Data and Use of Accepted Measures

PCORI encourages investigators to design their research using valid patient-centered outcomes measures and to include preliminary data that support the use of the proposed measures in the study population. Investigators are encouraged to consider those measures described in the *Patient Reported Outcomes Measurement Information System (PROMIS)*.⁵¹

Methodological Considerations

Regardless of study design, proposals must adhere to all relevant *PCORI Methodology Standards*.⁵² These include 47 individual standards that fall into 11 categories. The first five categories are cross-cutting and are relevant to most PCOR studies. Researchers should refer to all of these standards when planning and conducting their research projects. These five categories are:

- Standards for Formulating Research Questions
- Standards Associated with Patient-Centeredness
- Standards on Data Integrity and Rigorous Analyses
- Standards for Preventing and Handling Missing Data
- Standards for HTE

Six other categories of standards will be applicable to particular study designs and methods. The standards in each of these categories should be used for guidance when they are relevant to a particular study. These categories are:

- Standards for Data Registries
- Standards for Data Networks as Research-facilitating Infrastructures

⁵¹ Available at <http://www.nihpromis.org/>.

⁵² Available at <http://www.pcori.org/research-results/research-methodology/pcori-methodology-report/>.

- Standards for Causal Inference Methods
- Standards for Adaptive and Bayesian Trial Designs
- Standards for Studies of Diagnostic Tests
- Standards for Systematic Reviews

Most of these standards should be considered “minimal” standards. Additional best practices, including relevant guidelines for the conduct of clinical trials developed by other organizations, should be addressed in the application for PCORI funding. To help reviewers quickly identify the adherence to a particular standard, applicants must cite each methodology standard within their proposals as the standard is being addressed. For example, when applicants describe the need for their proposed study within the Background section, they should indicate the particular standard for Identify Gaps in Evidence in parentheses, such as “(RQ-1).”

All applicants should specifically discuss their capacity to measure such factors as differential adherence to chosen treatments (or participation in intervention programs) that could create or explain apparent differences in the effectiveness of the alternative interventions being compared in clinical populations.

Clinical Trial Design Guidance and Consultation

PCORI realizes that some applicants may not have extensive experience conducting large, real-world, comparative, pragmatic and patient-centered trial designs, nor in nontraditional designs such as adaptive designs. Applicants selected for funding may expect PCORI to seek and provide external expert statistical and trial design consultation in collaboration with the applicants at PCORI’s expense. The trial design consultation is a new initiative currently under development with the expectation that PCORI will put into place a capacity for trial design consultation in the coming year. This capacity includes experience and expertise in techniques such as trial design simulation and adaptive designs, and will serve to enhance the scientific rigor and efficiency of large pragmatic trials funded by PCORI.

Patient and Stakeholder Engagement

PCORI strongly supports active engagement of patient and other stakeholders and is committed to their meaningful participation in PCORI-funded research. All PCORI funding applicants are expected to consult with patients and other stakeholders on their decisional dilemma and evidence needs or reference previously documented decisional dilemmas in preparation for the submission of LOIs and applications. To describe the decisional dilemma, state the specific clinical decision(s) and treatment choice(s) confronted by the decision makers, and explain how the findings from the proposed research will inform those decisions. State why this decision, such as choosing between specific treatment strategies, is important to patients and their caregivers. Document the uncertainty faced by patients, clinicians, and other decision makers in making this decision. Identify the stakeholders you consulted in determining that the proposed study addresses their evidentiary needs for decision making, and indicate your commitment to continuing to engage them actively in the conduct of the study. Similarly, applicants should document why project outcomes are especially relevant to patients and should be meaningful endpoints for patients and their families.

PCORI has developed the [Engagement Rubric](#)⁵³ to guide the integration of patients and other stakeholders in the development, oversight, management, and implementation of research studies. Additionally, studies are expected to adhere to PCORI's [Methodology Standards](#) Associated with Patient-Centeredness and to the PCOR Engagement Principles found within the rubric. PCORI also has a [compensation framework](#)⁵⁴ for guidance on compensating individual patient partners on the research team. These and additional resources are available in [PCORI's Funding Center](#).

PCORI understands that applicants may not have the resources to establish formal partnerships prior to contract award, but expects applicants to discuss in their application their plan to work with PCORI to create the types of partnerships with national and regional patient and other stakeholder groups that will contribute to refinement of research questions, outcomes, protocols, and study conduct and dissemination.

Successful applicants are required to work in collaboration with PCORI staff upon award of the proposed studies to establish a project SAC (or other appropriate engagement body, see the [Treatment of Multiple Sclerosis FAQs](#)) that is comprised of national or regional organizations that represent, at a minimum, patients and families with lived experience, relevant clinicians, payers, and health plans. Other representation may be recommended in collaboration with PCORI, including individual patients with lived experience and other relevant stakeholders, among them scientific and methodological experts. The SAC serves to advise and assist the research team with further refinement of the study questions, outcomes, and protocol. It is expected that the SAC will meet regularly in person at least two times per year and may use virtual communications at other times. These are to be budgeted activities and represented in the project milestones.

Populations Studied

PCORI seeks to fund research that includes diverse populations with respect to age, gender, race, ethnicity, geography, or clinical status, so that possible differences in CER may be examined, otherwise known as HTE. PCORI recognizes that some proposed studies may represent important PCOR opportunities even in the absence of a broadly diverse study population. However, the burden is on the applicant in such cases to justify the importance of the study in the absence of diversity and to discuss which subgroups are most important and how they will be analyzed, including whether the study will be powered to examine the question of effectiveness in subgroups. PCORI is particularly interested in the inclusion of previously understudied populations for whom effectiveness information is especially needed, such as hard-to-reach populations or patients with multiple conditions. Thus, comparisons should examine the impact of the strategies in various subpopulations with attention to the possibilities that the effects of the strategy might differ across subpopulations. PCORI has developed a list of priority populations to guide our efforts in research and engagement:

- Racial and ethnic minority groups
- Low-income groups

⁵³ Available at <http://www.pcori.org/sites/default/files/Engagement-Rubric.pdf>.

⁵⁴ Available at <http://www.pcori.org/sites/default/files/PCORI-Compensation-Framework-for-Engaged-Research-Partners.pdf>.

- Women
- Children (age 0–17 years)*
- Older adults (age 65 years and older)
- Residents of rural areas
- Individuals with special healthcare needs, including individuals with disabilities
- Individuals with multiple chronic diseases
- Individuals with rare diseases
- Individuals whose genetic makeup affects their medical outcomes
- Patients with low health literacy and numeracy and limited English proficiency
- Lesbian, gay, bisexual, and transgender (LGBT) persons
- Veterans and members of the Armed Forces and their families

*Because pediatric MS poses a unique set of challenges regarding accuracy of diagnosis and safety and effectiveness of treatment, the April PCORI workshop did not specifically focus on this population. Applicants proposing studies of pediatric MS will need to address these additional challenges, providing assurances that the proposed comparisons reflect current common clinical practice.

Budget and Duration of Project

The following amounts to address each of the three questions:

Question 1 (DMTs) – up to \$10 million in total direct costs for a project period not to exceed five years

Question 2 (Non-DMT treatments for symptoms) – up to \$3 million in total direct costs for a project period not to exceed three years

Question 3 (Telerehabilitation) – Up to \$10 million in total costs for no more than two studies with total direct costs for any single study not to exceed \$5 million and a project period not to exceed four years

PCORI particularly encourages applicants to design projects that may be accomplished in less than five years. Note that PCORI will not cover costs for interventions that are being compared in the proposed study (see Appendix 3 in the [Application Guidelines](#) for details). Applicants should submit realistic budgets and timelines. For circumstances in which the estimated total direct costs exceed the limits, provide in your LOI a detailed justification that ties the extra expense to the importance and success of the project. Not all requests for additional funds will be approved. Any request for a project period longer than five years will be denied. For further information regarding PCORI's policies about allowable and unallowable costs, refer to Appendix 2 of the [Application Guidelines](#).

The funding mechanism for this program is a contract. Total project funding is contingent upon successful programmatic and budget performance (e.g., meeting recruitment targets). Milestones and

targets, as well as possible pilot phases for the sole purpose of assessing feasibility of recruitment, should be included in the budget and will be negotiated at the time of the award. Awardees will be expected to provide corroborating evidence to receive continual funding support. Some of the activities that will be considered during negotiations and subsequently include:

- Developing a study protocol and manual of procedures for the intervention
- Assigning roles and responsibilities of members of the study team for implementing the project
- Obtaining clearances from all institutional and community partners, including IRB approvals
- Establishing a DSMB or providing a clear description of why a DSMB is not considered necessary
- Executing all subcontractor agreements
- Identifying barriers to patient recruitment into the study and addressing these barriers effectively
- Demonstrating successful recruitment during a pilot phase (if indicated)

Refer to the Application Guidelines for a list of additional PFA-specific project milestones.

Collaboration

PCORI is particularly interested in applications that plan to involve community and commercial organizations that can help researchers design, implement, disseminate, and sustain effective interventions. We encourage applications that will include novel collaborations with accreditation organizations, credentialing bodies, educational enterprises, patient advocacy groups, industry, professional societies, and subspecialty societies.

Protection of Human Subjects

This component (up to five pages) is included in the Research Plan Template. Describe the protection of human subjects involved in your research. PCORI follows the Federal Policy for the Protection of Human Subjects (45 CFR part 46), including the Common Rule. For more detailed information, see Section 5 “Human Subjects Research Policy” from the [Supplemental Grant Application Instructions for All Competing Applications and Progress Reports](#),⁵⁵ issued by the US Department of Health and Human Services (HHS). PCORI does not require that applicants comply with sections of this policy that refer to requirements for federal-wide assurance (FWA), or that refer to standards for inclusion of women, minorities, and children. PCORI requires applicants proposing clinical trials to consider including a data- and safety-monitoring plan. Awardees must also comply with appropriate state, local, and institutional regulations and guidelines pertaining to the use of human subjects in research.

PCORI merit reviewers will examine plans for protection of human subjects in all applications and may provide comments regarding the plans (see [How to Evaluate Human Subjects Protections](#)⁵⁶). Reviewers’

⁵⁵ See <http://grants.nih.gov/grants/funding/424/supplementalinstructions.docx/>.

⁵⁶ See <http://www.pcori.org/sites/default/files/PCORI-Checklist-for-Evaluating-Human-Subjects-Protections.pdf/>.

comments on human subjects research are not reflected in the overall application score, but may be used by PCORI staff during any potential funding negotiations. Final determinations about adequacy of human subjects protections rest with the IRB or IRBs that have jurisdiction for the study.

The Awardee Institution or organization, whether domestic or foreign, bears ultimate responsibility for safeguarding the rights and welfare of human subjects in PCORI-supported activities.

Required Education of Key Personnel on the Protection of Human Subject Participants

PCORI requires all applicants to adhere to the National Institutes of Health (NIH) policy on education in the protection of human subject participants in the conduct of research. This applies to all personnel listed as Key Personnel in the application. The policy and FAQs are available [from the NIH website](#).⁵⁷

Replication and Reproducibility of Research and Data-Sharing Plan

PCORI is committed to maximizing the utility and usability of data collected in our funded projects. This is essential to building confidence in the accuracy of these findings. PCORI supports policies to promote sharing of study documentation (e.g., study protocol, programming code, and data definitions) so that other researchers may replicate the findings in other populations. Propose a method for sharing data and appropriate documentation upon request.

Peer Review and Release of Research Findings

PCORI has a legislative mandate to ensure the scientific integrity of the primary research it supports and to make study findings widely available and useful to patients, clinicians, and the general public within a specific timeframe. The PCORI Board of Governors (Board) adopted the following process for peer review and public release of the results of all funded studies.

Awardee Institutions are required to submit to PCORI for peer review a draft final research report that provides the methodological details, describes the main study results, and properly interprets the findings in clinical or other decisional contexts. Subject matter experts, individuals with expertise on research methodology or biostatistics, and patients, caregivers, and other healthcare stakeholders will review the draft final research report. After awardees have responded to reviewers' comments to PCORI's satisfaction, the report will be accepted and considered final. PCORI will then prepare a 500-word abstract summarizing the study results for patients and the general public, which the Awardee Institution will review and approve.

PCORI will post the following materials on its website no later than 90 days after the draft final research report is accepted: a 500-word abstract for medical professionals, a standardized summary of the study's results for patients and the general public, and a link to the study record on ClinicalTrials.gov (as applicable). The final research report, along with anonymized reviewer comments, will be made publicly available on the PCORI website no later than 12 months after its acceptance, except by prior mutual agreement with the Awardee Institution.

III. How To Submit an Application

⁵⁷ See <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-054.html>.

Letter of Intent

Applicants should download the [LOI template for the Multiple Sclerosis PFA](#) specifically for the Cycle 3 2015 Funding Cycle from the PCORI Funding Center. They must complete the document and convert it to a PDF with a four-page limit (not including references, which should be listed at the end). LOIs that exceed the page limit will **not** be reviewed. Do not upload additional documents as part of your LOI, such as letters of endorsements or support, as they are not requested at this stage. Their inclusion will result in LOI rejection without review. Visit the PCORI Funding Center for additional applicant resources, including the Application Guidelines and required templates.

Answer all of the questions in the LOI template. This includes the question on brief justification for the proposed cost of the study; providing an answer “the cost not to exceed \$20 million” is not sufficient. Then upload your document to PCORI Online. The deadline for LOI submission is November 12, 2015, by 5 p.m. (ET).

Letter of Intent Review

Only applicants whose LOIs are deemed most responsive to this PFA will be invited to submit a full application. LOIs are reviewed by a minimum of two PCORI staff and are not scored during review. Notification of denial or approval to submit an application will occur no later than December 18, 2015. Please refer to the [Application Guidelines](#) for information on how to submit your LOI via PCORI Online.

You are invited to submit an application based on the information provided in the LOI. Any changes to the following require PCORI's approval:

- Research question(s)
- Specific aims
- Study design
- Comparators
- Principal Investigator (PI)
- Institution

If you need to change any of this information or have any questions, email pfa@pcori.org.

Note: A PI may submit only one LOI for this PFA. An individual listed as a PI on one LOI may be listed and serve in another role (e.g., co-investigator, co-PI) on other LOIs.

Submission Dates

LOIs and applications must be submitted in accordance with the published dates and times listed in the overview of this PFA and in the [PCORI Funding Center](#).⁵⁸

PCORI Online

To submit a proposal, you must register with [PCORI Online](#)⁵⁹ and submit both an LOI and an application

⁵⁸ Available at <http://www.pcori.org/funding-opportunities/>.

⁵⁹ Available at <https://pcori.fluxx.io>.

for each cycle in which you are applying.

Applicant Resources

PCORI Funding Center	http://www.pcori.org/2015-Cycle-3-Multiple-Sclerosis
PCORI Online	pcori.fluxx.io
PCORI Funding Awards	pcori.org/pfaawards

IV. Merit Review

PCORI merit review is a multiphase process that includes:

- Evaluation of LOIs
- Inviting a subset of LOIs to submit full applications
- Administrative and programmatic review of full applications
- Preliminary review by review panels for full applications that meet administrative and programmatic requirements
- In-person review panel discussion of full applications
- In-person or webinar presentation by select applicants (at PCORI's discretion)
- Post in-person or webinar presentation, Selection Committee deliberation, and recommendation of applications for funding
- Board of Governors award approval (no later than July 2016)

Application Review Criteria

PCORI's review panels use the following five criteria during the preliminary and in-person phases to evaluate all submitted applications. Each application should address the listed questions.

Criterion 1. Potential for the study to fill critical gaps and generate actionable evidence

The proposal should address the following questions:

- Does the application convincingly describe clinical burden?
- Does the application clearly explain the decisional dilemma?
- Does the application identify a critical gap in current knowledge as noted in systematic reviews, guideline development efforts, or previous research prioritizations?
- Does the study identify variations in practice patterns that suggest clinical uncertainty?
- Does the application describe the decisional dilemmas experienced by patients and other stakeholders that this study would address?
- Does the study or application have the potential to fill these evidence gaps and inform

decision making for key stakeholders (provide example)?

Criterion 2. Potential for the study findings to be adopted into clinical practice and improve delivery of care

The application should describe how evidence that is generated from this study could be adopted into clinical practice and delivery of care by others. The application should address the following:

- Does the application identify potential end-users of study findings such as local and national stakeholders and incorporate strategies to engage these end-users in dissemination of outcomes? Does the application provide information that supports a demand for this kind of a study from end-users?
- How likely is it that positive findings could be reproduced by others, resulting in improvements in practice and patient outcomes? Identify the potential barriers that could hinder adoption of the intervention by others, including generalizability to other health systems or treatment settings, or complexity of the intervention, as applicable.
- Does the application describe a plan for how study findings will be disseminated beyond publication in peer review journals and national conferences?
- Can the study be readily adopted in other settings with minimal adaptations or complexities?

Criterion 3. Scientific merit (research design, analysis, and outcomes)

The application should show sufficient technical merit in the research design to ensure that the following study goals will be met:

- Does the proposal describe a clear conceptual framework to anchor the background literature and inform the design, key variables, and relationship between interventions and outcomes being tested?
- Does the application provide justification that the outcome measures are validated and appropriate for the population?
- Does the research plan describe rigorous methods that demonstrate adherence to PCORI's Methodology Standards?
- Are each of the comparators (e.g., active intervention arm and comparator arm) clearly described and well justified? If usual care is one of the arms, is it sufficiently justified and will it be sufficiently measured?
- Are the sample sizes and power estimates based on careful evaluations of the anticipated effect size? Is the effect size adequately justified in relation to the size or dose of the intervention and the research design (e.g., cluster randomized design)?
- Is the study plan feasible?
 - Is the project timeline realistic, including specific scientific and engagement milestones?

- Are planned start-up times realistic, including training of personnel? Have the investigators considered and addressed the potential barriers to study initiation within the targeted clinical setting?
- Is the strategy for recruiting participants feasible?
- Are assumptions about participant attrition realistic and are plans to address patient or site attrition adequate?

Criterion 4. Patient-centeredness

The application should demonstrate that the study focuses on improving patient-centered outcomes and employs a patient-centered research design (i.e., design is informed or endorsed by patients). *(Note: study can be patient-centered even if the end-user is not the patient, as long as patients will benefit from information.)* The proposal should address the following:

- Does the application include a thorough description about which outcomes (both benefits and harms) are important to patients and show that those outcomes are included in the study plan?
- Are the interventions being compared in the study available to patients now and are they the best options for comparison (including whether they would be chosen by patients and their healthcare providers for managing the condition being studied)?

Criterion 5. Patient and stakeholder engagement

The proposal describes plans for the engagement of and collaboration with relevant stakeholders (e.g., patients, caregivers, clinicians, hospitals and health systems, payers [insurance], purchasers [business], industry, researchers, policy makers, and training institutions) in the conduct of the study. PCORI understands that applicants may not have the resources to establish formal partnerships prior to contract award, but expects applicants to discuss in their application their plan to work with PCORI to create the types of partnerships with national and regional patient and other stakeholder groups that will contribute to refinement of research questions, outcomes, protocols, and study conduct and dissemination.

At a minimum, applicants shall plan to work in collaboration with PCORI staff upon award of the proposed studies to establish a project SAC (or other appropriate engagement body, see the [Treatment of Multiple Sclerosis FAQs](#)) that is comprised of national or regional organizations that represent, at a minimum, patients or families with lived experience, relevant clinicians, payers, and health plans. Other representation may be recommended in collaboration with PCORI, including individual patients with lived experience and other relevant stakeholders, among them scientific and methodological experts. The SAC serves to advise and assist the research team with further refinement of the study questions, outcomes, and protocol. It is expected that the SAC will meet regularly in person at least two times per year and may use virtual communications at other times. These are to be budgeted activities and represented in the project milestones. The proposal should address the following:

- Does the application provide a well-justified and comprehensive description of plans to build an interdisciplinary study team that includes appropriate patient and stakeholder representation?

- Are the plans for a strong partnership among scientists, patients and others throughout the entire research process (e.g., finalizing questions, identifying outcomes, monitoring study, dissemination and implementation) appropriate and tailored to the study?
- Are the scope, form, and frequency of patient and stakeholder involvement planned throughout entire research process sufficient to support the study goals?
- Are the roles and the decision-making authority of all study partners clearly described?
- Are the organizational structure and resources appropriate to carry out the project?

Preliminary Review

PCORI conducts rigorous merit review of the full applications it receives. Applications may be eliminated from the review process for administrative or programmatic reasons (i.e., nonresponsiveness). An application may be eliminated if it is incomplete or submitted past the stated due date and time, or if it does not meet the administrative or formatting criteria outlined in the Application Guidelines, in the PCORI templates, and in [PCORI Online](#).⁶⁰ It may also be withdrawn if it is not responsive to the guidelines described in this PFA, describes research that is not comparative, includes cost-effectiveness analysis, or otherwise fails to meet PCORI programmatic requirements. Per our authorizing legislation, if two proposed research plans overlap, funding preference must be given to applications submitted on behalf of NIH and the Agency for Healthcare Research and Quality (AHRQ).

One or more specially convened merit review panels will review responsive applications. PCORI Merit Review Officers (MROs) recruit each panel. MROs identify the chair, scientist reviewers who are clinical experts familiar with the clinical content of submitted applications, methodological and statistical experts familiar with PCTs and large database analyses, patient representatives trained in review of scientific proposals, and representatives of other stakeholder groups.

In-Person Review

After the preliminary review is completed, PCORI program staff members evaluate panel scores and critiques to identify a subset of applications to be discussed at the in-person review meeting. Not all submitted applications move forward to in-person review, but all applications are evaluated and scored based on PCORI's merit review criteria, which include evaluation of adherence to PCORI's Methodology Standards.

During the in-person review, panels meet to discuss applications and to clarify further the merits of the proposed research, as well as to identify areas for improvement. Additionally, each application is re-scored based on the content of discussion. The chair and PCORI MRO lead the in-person panel meeting and ensure that all applications receive a fair and thorough review informed by the standards outlined in the PFA.

In-Person Applicant Presentation

Based on the results of merit review and PCORI's programmatic priorities, a selective subset of applicants whose proposed studies are deemed to be highly meritorious and/or aligned with PCORI's

⁶⁰ Available at <https://pcori.fluxx.io/>.

strategic priorities may be invited to the second phase of project presentation and follow-up discussions with PCORI on study methodological and execution issues. Applicants are also expected to address concerns and critiques identified in the merit review in this presentation. The selected applicants will be notified of the logistics, including travel arrangements, for this presentation in separate communications.

Post-Panel Review

After the in-person panel review, PCORI program staff members evaluate merit review scores and comments, identify duplication or synergy among funded projects, and consider the fit of applications within the programmatic vision. Program staff members then recommend projects to a Selection Committee, which includes members of PCORI's Board. The Committee considers recommendations and works with staff to identify a slate of applications for possible funding based on merit review scores, programmatic balance and fit, and PCORI's strategic priorities. This slate is then proposed to PCORI's Board for its consideration and approval.

Summary Statements and Funding Recommendations

Summary statements are provided to applicants approximately two weeks before funding decisions are announced. If an application progresses to in-person discussion, the applicant will receive a summary statement inclusive of the panel discussion notes, the final average overall score, preliminary reviewer critiques and a quartile, which provides information for applicants to understand how they did relative to other discussed applications. Quartile 1 includes applications that score in the top 24 percent of discussed applications; quartile 4 includes applications that score in the bottom 25 percent of discussed applications.

Summary statements for applications that do not progress to in-person discussion include only the preliminary reviewer critiques.

Funding recommendations are made by identifying meritorious applications that fit the programmatic needs and that satisfactorily address the merit review criteria while adhering to PCORI's Methodology Standards. Programs also consider the funds allotted for the current funding announcement when deciding which applications to recommend to PCORI's Board for approval. Applicants to this current cycle's PFA will receive summary statements in late June 2016 and notification of the funding status of their application no later than July 2016.