



Cycle 3 2016 Funding Cycle

PCORI Funding Announcement Reopened: Treatment of Multiple Sclerosis

Published October 4, 2016
Updated May 19, 2017

This PCORI Funding Announcement (PFA) applies to the funding cycle that closes on February 7, 2017, at 5 p.m. (ET). Application Guidelines, templates, and other resources are available at <http://www.pcori.org/2016-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 and other stakeholders.

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, caregivers, clinicians, purchasers, policy makers, and other healthcare system stakeholders 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."

CLOSED

Patient-Centered Outcomes Research Institute

1828 L St., NW, Suite 900

Washington, DC 20036

Phone: 202-827-7700

Fax: 202-355-9558

Email: info@pcori.org

Follow us on Twitter: [@PCORI](https://twitter.com/PCORI)

Overview

Published	October 4, 2016
Updated	May 19, 2017
Letter of Intent Due	November 1, 2016, 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 2, 2016.
Summary	<p>The Patient-Centered Outcomes Research Institute (PCORI) seeks to fund randomized controlled trials (RCTs) or observational studies that compare two or more alternatives for the treatment of multiple sclerosis (MS), with a focus on the effects of therapies on the symptoms experienced by MS patients 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 (TR) versus conventional direct care on functional status, fatigue, and quality of life are of interest.</p> <p>Proposed studies must address important clinical and healthcare-delivery-related choices faced by patients, their caregivers, clinicians, or delivery systems. Proposed studies must compare two or more active interventions. They must involve patient populations that represent the U.S. population, be large enough to provide precise estimates of hypothesized effects, and support evaluation of potential differences in intervention effectiveness in different patient subgroups.</p> <p>For this solicitation, applicants are not required to demonstrate that patients and other stakeholders are already engaged as research team members at the time an application is submitted. However, applicants should outline how patients and other stakeholders will participate as partners in various phases of the proposed research, once awarded. Applicants should describe their plan to form a Study Advisory Committee (SAC),¹ or other appropriate engagement body, to ensure that a broad spectrum of patients and other stakeholders advise and assist the research team with refining the study questions, outcomes, and protocols. These patients and other stakeholders must include national or regional organizations that represent—at a minimum—patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders. Additional representation may be recommended in collaboration with PCORI, including individual patients with lived experience and other relevant stakeholders, such as scientific and methodological experts.</p> <p>Note that this funding program does not support applications to conduct cost-effectiveness analysis or systematic reviews. The proposed studies must address at least one of the priority research questions identified in the main body of the PFA.</p>
Applicant Resources	See http://www.pcori.org/2016-Cycle-3-Multiple-Sclerosis

¹ The intent of the SAC described in the PFA is to ensure that a broad spectrum of patients and other stakeholders advise and assist the research team with refining the study questions, outcomes, and protocols. These patients and other stakeholders must include national or regional organizations that represent—at a minimum—patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders. Additional representation may be recommended in collaboration with PCORI, including individual patients with lived experience and other relevant stakeholders, such as scientific and methodological experts. However, PCORI understands that engagement structures and approaches vary widely. Other engagement approaches, such as forming stakeholder groups, panels, task forces, working groups, and other bodies, or involving individual patient and other stakeholder partners in various ways, are also permissible to employ—either in addition to or instead of—the formation of the SAC. The SAC provision is not meant to require that a separate governance or advisory entity be established beyond the study governance and advisory structure the awardee has planned, if an applicant already has an approach for including the relevant and required patient and other stakeholder partners. For clarification in your application materials and merit review purposes, please indicate which body or structure is filling the SAC requirements for appropriate meetings and appropriate budgeting.

Key Dates	<p>PCORI Online System Opens: October 4, 2016</p> <p>Applicant Town Hall Session: October 11, 2016, 11 a.m. – 12:30 p.m. (ET)</p> <p>LOI Deadline: November 1, 2016, by 5 p.m. (ET)</p> <p>LOI Status Notification: December 2, 2016</p> <p>Application Deadline: February 7, 2017, by 5 p.m. (ET)</p> <p>Merit Review Dates: April 2017</p> <p>Awards Announced: September 12, 2017</p> <p>Earliest Project Start Date: November 2017</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 (TR): \$5M</p>
Maximum Research Project Period	<p>Question 1 (DMTs): 5 years</p> <p>Question 2 (symptomatic treatments): 3 years</p> <p>Question 3 (TR): 4 years</p>
Funds Available Up To	\$30 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; any laboratory or manufacturer; or any unit of local, state, or federal government. The Internal Revenue Service must recognize all U.S. applicant organizations. Nondomestic components of organizations based in the United States and foreign organizations may apply as long as there is demonstrable benefit to the U.S. healthcare system and U.S. efforts in the area of patient-centered research can be shown clearly. 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 in 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. Investigator(s) and environment 5. Patient-centeredness 6. Patient and stakeholder engagement
Contact Us	<p>Programmatic Inquiries: Contact the PCORI Helpdesk via email (sciencequestions@pcori.org) or 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 before 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. One week before an application deadline, 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	<p>Deadlines are at 5 p.m. (ET). If a deadline falls on a weekend or federal holiday, the deadline will be the following Monday or the next day after the federal holiday.</p>

NOTE FOR THIS REOPENED PFA:

- The Introduction of this document, including the scientific background, is unchanged from the PFA on Treatment of Multiple Sclerosis issued for Cycle 3-2015, except for the paragraph on Funds Available on page 12.
- Other changes in the PFA include:
 - i. Clarification about funds allocated for question 3 and about payment for the costs of healthcare system-based interventions is provided under Project Budget and Duration on page 19.
 - ii. In Section IV on Merit Review, a New Criterion 4 has been added and the section has been updated.
 - iii. The Replication and Reproducibility of Research and Data-Sharing Plan requirement during the application phase has been removed.
 - iv. Links to new [PCORI Policy on Data and Safety Monitoring Plans for PCORI-Funded Research](#) and [Process for Peer Review of Primary Research and Public Release of Research Findings](#) are now provided.
- Applicants are advised to review the awards that PCORI has [funded](#) on the treatment of MS to ensure that their proposed research complements those projects.
- PCORI may exercise discretion in selection of applications for funding within each of the three priority research areas stated in the PFA.

CLOSED

Table of Contents

I. Introduction	1
Summary of Program	1
Background	1
Research Topic Prioritization and Strategy	3
Priority Research Questions.....	3
Outcome Measures.....	5
Study Design Considerations	11
Funds Available (REVISED)	12
II. Guidance for Preparing Applications	12
Specific Requirements	12
Nonresponsiveness	14
Features of Patient-Centered Outcomes Research	15
Leveraging Existing Resources	15
Preliminary Data and Use of Accepted Measures	15
Methodological Considerations	16
Patient and Stakeholder Engagement	17
Populations Studied	18
Project Budget and Duration	18
Collaboration	20
Protection of Human Subjects.....	20
Required Education of Key Personnel on the Protection of Human Subject Participants	20
Data Management and Data-Sharing Plan	20
Peer Review and Release of Research Findings.....	21
III. How To Submit an Application	21
Letter of Intent.....	21
Letter of Intent Review	22
Submission Dates	23
PCORI Online.....	23
Applicant Resources.....	23
IV. Merit Review	23

Preliminary Review	24
In-Person Review	27
Post-Panel Review.....	28
Summary Statements and Funding Recommendations	28

CLOSED

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. In addition, applications should:

- Compare the effectiveness² of two or more alternatives for improving patient-centered outcomes.
- Include patient populations representative of people with MS.
- 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.³ The clinical course is highly variable, generally unfolding over decades, and symptoms and complications range from mild to the development of severe disability.

MS 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.⁴

In RRMS, the patient experiences acute attacks (relapses), followed by full or partial recovery. It is

² 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>).

³ Kamm, CP, Uitdehaag BM, Polman, CH. Multiple sclerosis: current knowledge and future outlook. *European neurology* 2014; 72:132-41.

⁴ Sadaka, Y, Verhey, LH, Shroff, MM, et al. 2010 McDonald criteria for diagnosing pediatric multiple sclerosis. *Annals of Neurology* 2012; 72:211-23.

estimated that 16–30 percent do not experience full recovery from their initial episode.⁵ 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.⁶

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.⁷ Fatigue is more common in people with MS than in the general population, affecting 33–75 percent of people with MS.⁸ 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.⁹

The evolution of RRMS to SPMS is highly variable,¹⁰ 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 2–5 years of onset are associated with a faster progression to a secondary-progressive course.¹¹

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 PPMS shows progression from the time of disease onset, whereas SPMS shows progression after initial presentation as RRMS. PRMS, the least common form, is associated with both acute relapses and continuing progression between relapses from the time of onset.

The goals of MS treatment 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,¹² and a recent systematic review of direct comparisons of even the oldest and most commonly used medications found insufficient evidence to draw conclusions about effects on patient-reported outcomes (PROs), such as quality of life.¹³

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

⁵ Confavreux, C, Vukusic, S. The clinical course of multiple sclerosis. *Handbook of clinical neurology* 2014; 122:343–69.

⁶ 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.

⁷ Kamm, CP, Uitdehaag, BM, Polman, CH. Multiple sclerosis: current knowledge and future outlook. *European neurology* 2014; 72:132–41.

⁸ Berger, JR, Pocoski, J, Preblick, R, Boklage, S. Fatigue heralding multiple sclerosis. *Multiple sclerosis* (Houndmills, Basingstoke, England) 2013; 19:1526–32.

⁹ 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/>.

¹⁰ Kantarci, OH, Weinshenker, BG. Natural history of multiple sclerosis. *Neurologic Clinics* 2005; 23:17–38.

¹¹ 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/>.

¹² 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/>.

¹³ 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.

relapses—mainly RRMS and PRMS.¹⁴ 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.¹⁵

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 MS research. 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 CER questions existed that could be addressed by PCORI-funded research. More than 40 invited stakeholders attended the final and largest [workshop](#)¹⁶ 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 the following four categories: (1) comparison of DMTs, including differential effects in subgroups; (2) care strategies; (3) nonpharmacologic and non-DMT therapy for specific symptoms and overall health; and (4) timing of therapy and study design. The participants discussed, revised, and ranked these questions 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.

PCORI's Board of Governors (Board) reviewed and approved the research questions for this PCORI Funding Announcement (PFA) on September 28, 2015.

Priority Research Questions

Applications must propose randomized controlled trials (RCTs) and observational studies that address one of the priority research questions listed on the following page. 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 MS, 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.

¹⁴ Medications. (n.d.). Retrieved May 7, 2015, from <http://www.nationalmssociety.org/Treating-MS/Medications/>.

¹⁵ 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).

¹⁶ Available at <http://www.pcori.org/events/2015/prioritizing-comparative-effectiveness-research-questions-treatment-multiple-sclerosis>.

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 RRMS 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 (TR) 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 TR interventions to enhance community-based primary care or neurology practice for patients who do not have access to specialty centers. Applications that employ interventions already in practice are especially attractive.
 - Studies should examine the impact of the TR 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 RRMS 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 syndromes may be included with appropriate justification in a study of initial DMT. treatment

There are now 12 FDA-approved DMTs to treat MS,¹⁷ including three oral therapies that have been introduced since 2010.¹⁸ There is a lack of consensus about what constitutes best initial therapy,^{19, 20} and

¹⁷ Medications. (n.d.). Retrieved May 7, 2015, from <http://www.nationalmssociety.org/Treating-MS/Medications/>.

¹⁸ 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.

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 RRMS treatments.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 MS 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 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 MS treatments is the lack of scales to assess disability,²³ which has led to the creation of a public-private partnership between the FDA, the

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.

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 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.

European Medicines Agency, and industry to create sensitive, clinically meaningful, and reliable outcome measures to use in MS clinical trials.²⁴ In early deliberations of this group, it was noted that outcomes other than disability are also important to patients, including pain, fatigue, bladder dysfunction, and impacts on cognitive function.

The most widely used scale to measure disability in MS studies is the Expanded Disability Status Scale (EDSS). Although 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 inclusion of 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 ensure that outcomes are patient-centered, correlate with accepted clinical outcome measures, and adhere to the PCORI 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.

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 MS 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, tremors, 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, selective serotonin reuptake inhibitors (SSRIs), aspirin, modafinil, dextroamphetamine salts, lisdexamfetamine

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.

Symptom	Commonly Used Treatment Options
	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, oxcarbamazepine, duloxetine, tricyclic antidepressants, lidoderm patches, capsaicin cream are effective.
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
Bladder problems	Pharmacologic: Onobotulinumtoxin A, desmopressin, tolterodine, oxybutynin, darifenacin, tamsulosin, terazosin, prazosin, propantheline, trospium chloride, imipramine, solifenacin 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

Symptom	Commonly Used Treatment Options
Cognitive changes	Pharmacologic: Interferon, donepezil, galantamine, modafanil, 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 MS symptoms 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 symptom and compared strategies by documenting both the symptom’s importance 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 ensure that outcomes are patient-centered, correlate with accepted clinical outcome measures, and adhere to the PCORI Methodology Standards.

Question 3. What is the comparative effectiveness of TR 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 TR interventions to enhance community-based primary care or neurology practice for patients who do not have access to specialty centers. Applications that employ interventions already in practice are especially attractive.
- Studies should examine the impact of the TR strategies in various subpopulations, including individuals with low socioeconomic status and patients with progressive disease.

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.

MS is a chronic condition of the central nervous system with heterogeneous clinical manifestation. Thus, the care of MS patients 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 MS patients at onset and chronic in 80 percent of cases.³¹ Balance and PC disorders in MS patients 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 resulting 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 treatment barriers.³³ In response to this situation, interest has recently increased with regard to the development of eHealth projects. In the context of eHealth, TR is the delivery of rehabilitation services via 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 prime for CER.^{35,36}

Prior evaluations have demonstrated the success of various TR interventions at improving outcomes for MS patients.

- Finkelstein et al. (2008) found that a home-based physical TR can improve functional outcomes in MS patients. The study participants also demonstrated a very high level of support for the home-based physical TR program.³⁷
- Frevel et al. (2015) found that an Internet-based home training program had positive impacts on improving balance in MS patients. The study results 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 PC among MS patients who completed a virtual-reality-system TR program.³⁹

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.

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.

- Finlayson et al. (2011) reported a significant reduction in fatigue among MS patients who completed a group-based, teleconference-delivered fatigue-management program, compared to a wait-list control group.⁴⁰

Despite the demonstrated success of various TR interventions at improving outcomes for MS patients and the growing number of studies evaluating various interventions of TR for persons with MS, the evidence base for their effectiveness has important gaps. There is insufficient evidence to indicate what types of TR 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 Treatment Effect (HTE) for different groups of MS patients, including those who are geographically remote or of lower socioeconomic status and who have progressive disease. Recent systematic reviews call for more robust trials to build the evidence base for the clinical effectiveness of these interventions.^{41,42}

In response, PCORI seeks to fund studies that compare TR models of care to conventional direct care for MS patients. 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 socioeconomic status. PCORI is not interested in proposals to study the efficacy of a new TR model; acceptable models must have established efficacy or effectiveness. TR 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 TR interventions 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.

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.

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

⁴² Amaty, 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.

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 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 using innovative observational methods such as dynamic marginal structural modeling⁴³ and machine learning.^{44,45}

RCTs 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 biomarkers⁴⁹—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.

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.

Funds Available (REVISED)

PCORI will devote up to \$30 million in total costs under this PFA. Please see the Project Budget and Duration section for details.

Given the significant implementation costs associated with some interventions, the applications must specifically address—in the context of the proposed studies—the support from payers, health plans, industry sponsors, or others in covering the study interventions and non-study, protocol-related clinical costs and services rendered in the care processes. Of particular concern would be different levels of co-payment between two arms in a comparative study. Ideally, cost-sharing barriers will be eliminated or equalized in the study arms. If the study design does not allow this, the applicant should describe why and discuss how differences in co-payment costs will be accounted for in the analysis of the study's findings.

It is expected that project budgets and duration will vary substantially, depending on the topic and approach selected, needs for recruitment or 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; registries; research cooperatives; and the supportive involvement of delivery systems or health plans to enhance recruitment, data collection, and coverage of intervention-related costs. A prolonged recruitment period is not an acceptable rationale for longer studies. Funding requests to develop or build on initial collaboration between researchers and patient/stakeholder groups are also not appropriate for this PFA.

II. Guidance for Preparing Applications

Specific Requirements

The proposed study should strive to meet the following requirements:

- Focus on a comparative effectiveness question that is important to patients and other decision makers.
- Address a research gap that has been substantiated by an existing (recent or updated), rigorously conducted systematic review or emphasized by an official professional society's clinical practice guideline.
- Demonstrate consultation with patients and other stakeholders or their representative groups, or reference previously documented decisional dilemmas to determine if the study is answering a critical question—one that, if adequately answered, would substantially improve decision making.
- Receive endorsement by relevant patient organizations, clinician organizations, payer or purchaser consortia, or life sciences industry representatives as potentially 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. The sample size must also support testing of *a priori* hypotheses related to potential

differences in effectiveness among relevant patient subgroups (HTE).

- Examine diverse populations receiving care in real-world settings.
- Have strong interest from and support of host delivery systems and clinical care settings.
- Specify broad and simple eligibility criteria that will allow wide generalization of results while attending appropriately to ethical concerns of excess risk in some patient subgroups.
- As applicable, compare interventions that are known to be efficacious, effective, or commonly used and that can be implemented in real-world settings.
- Include PROs as primary outcomes, 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 present evidence that the study will not encounter significant barriers to recruitment or participation. The relevant IRBs make the final determination of the adequacy of informed consent procedures and participant protections.
- Adhere to all applicable [PCORI Methodology Standards](#).⁵⁰ The full application will require the applicant to identify the standards appropriate to the proposed study and describe how the study team plans to address each standard.
- In the case of RCTs, also adhere to current best practices (standardized inclusion or exclusion criteria; proper randomization; techniques to minimize potential for missing data; and appropriate safety monitoring, including establishment of a Data and Safety Monitoring Board [DSMB] or indication of why such a board is unnecessary).
- For observational studies, employ rigorous designs that can address concerns related to causal inferences about the relative effectiveness of different strategies on patient-centered outcomes. Applications will need to make a clear conceptual and analytical connection between interventions, comparators, and patient-centered outcomes. Investigators should carefully consider and justify the appropriate observational design for their question, which may include opportunistic, natural experiments or other observational research approaches using longitudinal, quasi-experimental study designs. Proposals using cross-sectional or simple pre-post designs are discouraged.
- Be prepared to identify and engage with major patient and stakeholder organizations that would implement study findings, as well as with existing local communities of patients and care providers, to refine the research questions and study protocol, help monitor progress, and disseminate the findings.

⁵⁰ Available at [pcori.org/research-we-support/research-methodology-standards/](https://www.pcori.org/research-we-support/research-methodology-standards/).

To carry out CER studies, readily adopt the findings in a real-world setting, and maximize the efficient use of resources, applicants must prevent these trials from becoming more complex and onerous than necessary. PCORI encourages the applicant to be creative and consider the following innovative strategies, 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 submitting Letters of Intent (LOIs) and the full applications.
- Describe carefully the pertinent evidence gaps and why the project questions represent decisional dilemmas for patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders. Similarly, applicants should document why project outcomes are especially relevant and meaningful endpoints for patients and other stakeholders. Minimize disruption to participants' daily routines (e.g., minimize participant visits intended for study-assessment purposes; capture PROs during office visits, electronically, or by phone).
- Design the study so that the conduct can integrate 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 (EHRs) and other computerized information to identify and recruit eligible patients, monitor study conduct and patient safety, and collect study outcomes information. PCORI specifically encourages applications that use the National Patient-Centered Clinical Research Network (PCORnet) infrastructure.
- 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 EHR systems.

Nonresponsiveness

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

- Aims to establish the efficacy of a new intervention
- Conducts a cost-effectiveness analysis in the form of dollar-cost per quality-adjusted life-year to compare two or more alternatives
- Directly compares the costs of care between two or more alternative approaches
- Measures the relative costs of care of two or more alternative approaches as the primary criteria for choosing the preferred alternative
- Conducts studies of the natural history of disease, instrument development, pharmacodynamics, and fundamental science of biological mechanisms
- Proposes a pilot study intended to inform larger efforts

- Develops clinical prediction or prognostication tools
- Develops clinical practice guidelines

Please also keep in mind that applications may measure and report use of any or all health services, but may not employ direct measurements of care costs.

PCORI does have an interest, however, in studying conditions that lead to high costs to the individual or to society. Thus, PCORI is also interested in studies that do the following:

- 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.

Applications that include studies of these issues without using cost-effectiveness analyses or comparing the costs of alternatives are considered responsive.

Features of Patient-Centered Outcomes Research

PCORI funds patient-centered outcomes research (PCOR), which helps people 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, and monitoring strategies 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 (including 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 available in the clinical settings
- Obtains stakeholder perspectives to address the burdens to individuals, availability of services, and technology and personnel requirements

Leveraging Existing Resources

PCORI encourages investigators 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 and relevant information that may be used to answer important CER questions. Studies that leverage existing research networks or consortia that would facilitate the conduct of large, multi-site studies called for in this funding announcement are of interest.

Preliminary Data and Use of Accepted Measures

PCORI encourages investigators to design their research using valid patient-centered outcomes measures. Include preliminary data that support using the proposed measures in the study population. We encourage investigators to consider those measures described in the [Patient-Reported Outcomes](#)

Measurement Information System (PROMIS).⁵¹

Methodological Considerations

Regardless of study design, applications must adhere to all relevant [PCORI Methodology Standards](#).⁵² These include 47 individual standards that fall into 11 categories. The first five categories are crosscutting and relevant to most PCOR studies. Researchers should refer to all of these standards when planning and conducting their research projects. These crosscutting categories are:

1. Standards for Formulating Research Questions
2. Standards Associated with Patient-Centeredness
3. Standards on Data Integrity and Rigorous Analyses
4. Standards for Preventing and Handling Missing Data
5. Standards for Heterogeneity of Treatment Effect (HTE)

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

1. Standards for Data Registries
2. Standards for Data Networks as Research-Facilitating Infrastructures
3. Standards for Causal Inference Methods
4. Standards for Adaptive and Bayesian Trial Designs
5. Standards for Studies of Diagnostic Tests
6. Standards for Systematic Reviews

Most of these standards are minimal. The PCORI Methodology Standards reflect practices that should be followed in all cases, and all deviations need to be explained and well justified. Additional best practices—including relevant guidelines for conducting 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 relevant PCORI Methodology Standard within their applications as the standard is being addressed. For example, when applicants describe the need for their proposed study in the Background section, they should indicate the particular standard to identify evidence gaps in parentheses, such as “(RQ-1).”

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.

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

⁵² Available at pcori.org/research-we-support/the-pcori-methodology-report/.

Patient and Stakeholder Engagement

PCORI encourages all applicants to outline how patients and other stakeholders will participate as partners in various phases of the proposed research. Before completing this section of the Research Strategy, applicants are encouraged to review [PCORI's Engagement Rubric](#),⁵³ which can be found in the PCORI Funding Center. Applicants should also review the PCORI Methodology Standards Associated with Patient-Centeredness and [PCORI's Sample Engagement Plans](#).⁵⁴ The rubric and Sample Engagement Plans are not intended to be comprehensive or prescriptive; instead, they provide a variety of examples to incorporate engagement, where relevant, into the research process.

Applicants are expected to consult with patients and other stakeholders on their decisional dilemma and evidence needs or to 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) or 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 a specific medication, surgical approach, or care delivery strategy to treat a condition or manage a specific population—is important to patients. Document the uncertainty patients and other stakeholders face in making this decision. Identify the patients and other stakeholders you consulted in determining that the proposed study addresses their evidentiary needs for decision making, and indicate your commitment to continue engaging them actively in the conduct of the study. Similarly, applicants should document how the project outcomes are especially relevant and meaningful endpoints to patients and other stakeholders.

For this PFA, applicants are not required to demonstrate that patients and other stakeholders are already engaged as research team members at the time an application is submitted. However, the Engagement Plan should outline how patients and other stakeholders will participate as partners in various phases of the proposed research, once awarded. Applicants should describe their plan to form a Study Advisory Committee (SAC), or other appropriate engagement body, to ensure that a broad spectrum of patients and other stakeholders advise and assist the research team with refining the study questions, outcomes, and protocols. These patients and other stakeholders must include national or regional organizations that represent—at a minimum—patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders. Additional representation may be recommended in collaboration with PCORI, including individual patients with lived experience and other relevant stakeholders, such as scientific and methodological experts. The SAC or other appropriate engagement body should meet regularly, and the budget should account for these engagement costs.

PCORI understands that engagement structures and approaches vary widely. Other engagement approaches, such as forming stakeholder groups, panels, task forces, working groups and other bodies or involving individual patient and other stakeholder partners in various ways, are also permissible to employ—either in addition to or instead of—the formation of the SAC. For clarification in your application materials and for merit review purposes, please indicate which body or structure is filling the SAC requirements, including the requirements for regular meetings and appropriate budgeting.

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

⁵⁴ Available at <http://www.pcori.org/sites/default/files/PCORI-Sample-Engagement-Plans.pdf>.

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 comparative effectiveness of the interventions may be examined (otherwise known as HTE). PCORI recognizes that some proposed studies might 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 study's importance in the absence of diversity. The applicant must also discuss which subgroups are most important and how they will be analyzed, including whether there will be power to examine the question of effectiveness in subgroups. PCORI is particularly interested in including 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 possibility that the strategy's effects might differ across subpopulations. PCORI has developed the following list of priority populations to guide our research and engagement efforts:

- Racial and ethnic minority groups
- Low-income groups
- 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, numeracy, or limited English proficiency
- Lesbian, gay, bisexual, and transgender (LGBT) persons
- Veterans and members of the Armed Forces and their families

Project Budget and Duration

The following amounts are available 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
- **REVISED** Question 3 (TR)—up to \$5 million in total direct costs for a project period not to exceed

four years

At the time of contract execution, PCORI sets aside all of the funds associated with an awarded project to be made available throughout the contract's period of performance. Obligated funding is available for the duration of the project period. Note that, in general, PCORI will not cover costs for interventions that are being compared in the proposed study. (See Appendix 2 in the [Application Guidelines](#) for details.) However, in cases where this policy would preclude conducting a CER study that addresses the priority questions outlined in this PFA, such as research on providing telehealth services in underserved or hard-to-reach populations or settings, PCORI may consider a waiver on this policy. In such cases, the applicant will need to address the issue of scalability, sustainability, and potential for broad dissemination of the intervention beyond the project period. The applicant should also demonstrate that payers and health systems will likely cover the intervention costs if study results demonstrate its effectiveness. Request for such a waiver and the accompanying justification must be made in the LOI, and PCORI staff must approve the waiver at the LOI stage before a full application is submitted.

Applicants should propose realistic budgets, project duration, and associated timelines. For those rare circumstances in which the estimated direct cost exceeds the maximum direct costs outlined in this PFA, please provide a detailed justification in your LOI that ties the extra expense to the project's success. 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. Note that although subcontractor indirect costs are included in the prime applicant's direct-cost budget, subcontractor indirect costs are not factored when determining adherence to the PFA's direct-cost limit.

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 recruitment feasibility, 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 include:

- Developing a study protocol and procedure manual for the intervention
- Assigning roles and responsibilities to study team members for implementing the project
- Forming a SAC or other appropriate engagement body
- 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 necessary
- Executing all subcontractor agreements
- Agreeing on eligible patient populations for study recruitment
- Identifying barriers to patient recruitment in 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 involve community and commercial organizations that can help researchers design, implement, disseminate, and sustain effective interventions. We encourage applications that 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 proposed research. PCORI follows the Federal Policy for the Protection of Human Subjects ([45 CFR part 46](#)), including the Common Rule. For more detailed information, please see Section 5, titled “Human Subjects Research Policy,” in the [Supplemental Grant Application Instructions for All Competing Applications and Progress Reports](#),⁵⁵ which is issued by the U.S. Department of Health and Human Services. PCORI does not require that applicants comply with sections of this policy that refer to requirements for federal-wide assurance or that refer to standards for including women, minorities, and children. Awardees must also comply with appropriate state, local, and institutional regulations and guidelines pertaining to the use of human subjects in research.

PCORI requires awardees to ensure that there is a Data and Safety Monitoring Plan (DSMP), which may include the need to appoint a DSMB, as provided in the [PCORI Policy on Data and Safety Monitoring Plans for PCORI-Funded Research](#).⁵⁶

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](#)⁵⁷). Reviewers’ comments on human subject research are not reflected in the overall application score, but PCORI staff might use them during potential funding negotiations. Final determinations about the adequacy of human subject protections rest with the IRB or international equivalent that has jurisdiction for the study.

The Awardee Institution, 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 individuals listed as key personnel in the application. The policy and FAQs are available on the [NIH website](#).⁵⁸

Data Management and Data-Sharing Plan

PCORI encourages openness in research and making research data available for purposes of replication

⁵⁵ See <http://grants.nih.gov/sites/default/files/supplementalinstructions.docx>.

⁵⁶ See <http://www.pcori.org/sites/default/files/PCORI-Policy-Data-Safety-Monitoring-Plans.pdf>.

⁵⁷ See <http://www.pcori.org/sites/default/files/PCORI-Checklist-for-Evaluating-Human-Subjects-Protections.pdf/>.

⁵⁸ See <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-054.html>.

and reproducibility. Although not required to be submitted as a component of the research application, if an award is made, the awardee is required to develop and maintain a plan that addresses data management and data sharing of research project data in a manner that is appropriate for the nature of the research project and the types of research project data, and that is consistent with applicable privacy, confidentiality, and other legal requirements.

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. Accordingly, the Board adopted the [Process for Peer Review of Primary Research and Public Release of Research Findings](#).⁵⁹

In summary, 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 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 Awardee Institutions 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: (1) a 500-word abstract for medical professionals; (2) a standardized summary of the study results for patients and the general public; (3) a link to the study record on [ClinicalTrials.gov](#) (as applicable); and (4) ancillary information, including conflict of interest disclosures. 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

Letter of Intent

Applicants should download the [Cycle 3 2016 Multiple Sclerosis LOI Template](#) from the PCORI Funding Center. They must complete the document and convert it to a PDF with a four-page limit. PCORI suggests including all references as in-text citations using American Medical Association citation style, but other citation styles are accepted. Do not upload additional documents as part of your LOI, such as Letters of Endorsement or Support, because they are not requested at this stage. Their inclusion will result in LOI rejection without review. Please visit the PCORI Funding Center for additional applicant resources, including the PFA and required templates.

Please answer all of the questions in the LOI Template. This includes the question on brief justification for the proposed cost of the study. Providing the answer "costs not to exceed \$6 million" is not

⁵⁹ See <http://www.pcori.org/sites/default/files/PCORI-Peer-Review-and-Release-of-Findings-Process.pdf>.

sufficient. Upload your document to PCORI Online. The deadline for LOI submission is November 1, 2016, by 5 p.m. (ET).

Letter of Intent Review

LOIs are evaluated based on the following criteria:

- Whether the proposed topic addresses the priority research question identified in this funding announcement
- Importance of the specific research question (comparison), as evidenced by critical gaps identified by clinical guidelines developers or recent relevant systematic reviews
- A size or scope sufficient enough to have a significant impact on patient outcomes or healthcare practices
- Clarity and credibility of the applicants' responses to the LOI questions, as well as their justification of the proposed study size, citing published estimates, including effect sizes, standard deviations, and the need for rigorous comparative analysis of important subgroups
- Prior relevant experience
- Programmatic fit and balance, considering whether the research study question and study design are compliant with requirements in this PFA
- Adherence to the administrative and formatting requirements listed in the Application Guidelines, specifically the four-page limit for the LOI

Only applicants whose LOIs are deemed most responsive to this PFA will be invited to submit a full application. Notification of denial or approval to submit an application will occur no later than December 2, 2016. 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 approval:

- Research question(s)
- Specific aims
- Study design
- Comparators
- Principal Investigator (PI) (Contact PI and PI #2)
- Institution

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

Note: A PI can only submit one LOI per PFA. However, an individual listed as a PI on one LOI may be listed as and serve in another non-PI role (e.g., co-investigator, co-PI, or consultant) on other LOIs within the same PFA during the same cycle. A PI may submit multiple LOIs to different program PFAs in a cycle,

but the PI must ensure that the research topics and projects are not similar. If a PI submits an LOI to multiple program PFAs, LOIs that exhibit scientific overlap or that appear to be duplicate submissions will be disqualified. PCORI will contact the PI and provide him or her with an opportunity to choose which PFA he or she would like to apply to. This applies to single- and dual-PI submissions.

Submission Dates

LOIs and applications must be submitted in accordance with the published dates and times listed in the Overview section of this document and in the [PCORI Funding Center](#).⁶⁰

PCORI Online

To submit an application, you must register with [PCORI Online](#)⁶¹ and submit an LOI and an application for each cycle in which you are applying.

Applicant Resources

PCORI Funding Center	http://www.pcori.org/2016-Cycle-3-Multiple-Sclerosis
PCORI Online System	pcori.fluxx.io
PCORI Funding Awards	http://www.pcori.org/research-results-home

IV. Merit Review

PCORI's merit review process is designed to support the following goals:

- Identify applications that have the strongest potential to help patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders make informed decisions to improve patient outcomes.
- Implement a transparent, fair, objective, and consistent process to identify these applications.
- Elicit high-quality feedback that reflects a diversity of perspectives to ensure that the PCORI-funded research reflects the interests and views of patients and other stakeholders and those who care for them, and that it meets the criteria for scientific rigor.
- Fund projects that fill important evidence gaps and have strong implementation potential.
- Regularly evaluate and continually improve the merit review process and policies in support of PCORI's mission.

PCORI merit review is a multiphase process that includes PFA development; staff evaluation of LOIs; the review panel's preliminary review of full applications; an in-person panel discussion of a subset of full applications (identified by PCORI's Research Priority Area Program staff and based on the preliminary review and program priorities); the Selection Committee's recommendation of applications for funding;

⁶⁰ Available at pcori.org/apply.

⁶¹ Available at pcori.fluxx.io.

and, finally, Board award approval.

Preliminary Review

PCORI conducts rigorous merit review of the full applications it receives. Note that PCORI may eliminate applications from the review process for administrative or scientific reasons (e.g., nonresponsiveness). An application may be administratively withdrawn if it is incomplete; submitted past the stated due date and time; or does not meet the formatting criteria outlined in the [Application Guidelines](#), in the PCORI templates, and in PCORI Online. An application can be scientifically withdrawn if it is not responsive to the guidelines described in this PFA, describes research that is not comparative, includes a cost-effectiveness analysis, or otherwise does not meet PCORI programmatic requirements.

PCORI Merit Review Officers (MROs) recruit each panel based on the number of areas and topics represented by invited LOIs. MROs recruit the panel chair, scientist reviewers who are subject matter experts, patient representatives, and representatives of other stakeholder groups. All panel members receive training during the review cycle to ensure that they understand the programmatic and organizational goals of review.

The table on the next page is designed to help applicants understand how the PCORI merit review criteria align with criteria from other funding organizations with which applicants might be familiar (e.g., NIH). Though PCORI’s criteria do map to most NIH criteria, there are areas where we ask for different information (i.e., PCORI does not include a criterion that tracks to NIH’s innovation criterion, but does include criteria evaluating patient-centeredness and engagement) reflecting PCORI’s unique approach.

Crosswalk of PCORI Merit Review Criteria with NIH Criteria	
SIGNIFICANCE	<ol style="list-style-type: none"> 1. Potential for the study to fill critical gaps in evidence 2. Potential for the study findings to be adopted into clinical practice and improve delivery of care
APPROACH	<ol style="list-style-type: none"> 3. Scientific merit (research design, analysis, and outcomes) NEW 4. Investigator(s) and environment
PCORI-only Merit Review Criteria	
PATIENT-CENTEREDNESS/ENGAGEMENT	<ol style="list-style-type: none"> 5. Patient-centeredness 6. Patient and stakeholder engagement

Below are PCORI’s merit review criteria. PCORI’s merit review panels use these criteria during the preliminary and in-person review phases to evaluate and score all submitted applications and to ensure consistency and fairness in how applications are evaluated.

Criterion 1. Potential for the study to fill critical gaps in evidence:

The application should address the following questions:

- Does the application convincingly describe the clinical burden?

- Does the application identify a critical gap in current knowledge as noted in systematic reviews, guideline development efforts, or previous research prioritizations?
- Does the application identify a critical gap in current knowledge, evidenced by inconsistency in clinical practice and decision making?
- Would research findings from the study have the potential to fill these evidence gaps?

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

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

- Does the application identify who will make the decision (i.e., the decision maker) or use (i.e., the end-user) the study findings (not the intervention) this study produces, such as local and national stakeholders?
- Does the application identify potential end-users of study findings—such as local and national stakeholders—and describe strategies to engage these end-users?
- Does the application provide information that supports a demand for this kind of a study from end-users?
- Would this study’s research findings have the potential to inform decision making for key stakeholders? If so, provide an example. 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.
- Does the application describe a plan for how study findings will be disseminated beyond publication in peer-review journals and at national conferences?

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

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

- Does the application describe a clear conceptual framework anchored in background literature which informs the design, key variables, and relationship between interventions and outcomes being tested?
- Does the Research Plan describe rigorous methods that demonstrate adherence to the PCORI Methodology Standards?
- Is the overall study design justified?
- Are the patient population and study setting appropriate for the proposed research question?
- Does the application provide justification that the outcome measures are validated and appropriate for the population?

- Are each of the comparators (e.g., active intervention arm and comparator arm) described clearly and well justified? If “usual care” is one of the arms, is it adequately justified and will it be sufficiently measured?
- Are the sample sizes and power estimates appropriate? Is the study design (e.g., cluster randomized design, RCT, observational study) accounted for and anticipated effect size adequately justified?
- Is the study plan feasible? Is the project time line realistic, including specific scientific and engagement milestones? Is the strategy for recruiting participants feasible? Are assumptions about participant attrition realistic, and are plans to address patient or site attrition adequate?

NEW Criterion 4. Investigator(s) and environment

This criterion should assess the appropriateness (e.g., qualifications and experience) of the investigator(s)/team and the environment’s capacity (e.g., resources, facilities, and equipment) to support the proposed project. It should not be an assessment of the institution’s quality.

The application should also address the following questions:

- How well qualified are the PIs, collaborators, and other researchers to conduct the proposed activities? Is there evidence of sufficient clinical or statistical expertise (if applicable)?
- Does the investigator or co-investigator have demonstrated experience conducting projects of a similar size, scope, and complexity?
- If the project is collaborative or dual-PI, do the investigators have complementary and integrated expertise? Are the leadership, governance, and organizational structures appropriate for the project?
 - (Dual-PI option only) Does the Leadership Plan adequately describe and justify PI roles and areas of responsibility?
- Is the level of effort for each team member appropriate for successfully conducting the proposed work?
- Does the application describe adequate availability of and access to facilities and resources (including patient populations, samples, and collaborative arrangements) to carry out the proposed research?
- Is the institutional support appropriate for the proposed research?

Criterion 5. Patient-centeredness

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

The application should also address the following questions:

- Does the application include a thorough description about which outcomes (both benefits and

harms) are important to patients, and are those outcomes included in the study plan?

- Does the application provide information that indicates that closing the evidence gap is important to patients and other stakeholders?
- 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 6. Patient and stakeholder engagement

The application should demonstrate the engagement of relevant patients and other stakeholders (e.g., patients, caregivers, clinicians, policy makers, hospitals and health systems, payers [insurance], purchasers [business], industry, researchers, and training institutions) in the conduct of the study. Quality of engagement should be evaluated based on scope, form, and frequency of patient and stakeholder involvement throughout the research process.

The application should also address the following questions:

- Does the application provide a well-justified description of how the research team incorporates stakeholder involvement? Does the study include the right individuals (e.g., researchers, patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders) to ensure that the projects will be carried out successfully?
- Does the application show evidence of active engagement among scientists, patients, and other stakeholders throughout the research process (e.g., formulating questions, identifying outcomes, monitoring the study, disseminating, and implementing)? Are the frequency and level of patient and stakeholder involvement sufficient to support the study goals?
- Is the proposed Engagement Plan appropriate and tailored to the study?
- Are the roles and the decision-making authority of all study partners described clearly?
- Are the organizational structure and resources appropriate to engage patients and stakeholders throughout the project?

In-Person Review

During preliminary review, all administratively and scientifically compliant applications are evaluated and scored based on PCORI's merit review criteria, including evaluation of adherence to the PCORI Methodology Standards. After PCORI completes the preliminary review, PCORI program staff members evaluate panel scores and critiques to identify a subset of applications for merit reviewers to discuss at the in-person review meeting. Not all submitted applications move forward to in-person review.

During the in-person review, merit reviewers meet to discuss applications and to clarify further the merits of the proposed research. They also identify areas for improvement. Each application is re-scored based on the content of discussion. The Panel Chair and PCORI MRO lead the in-person panel meeting and ensure that all applications receive a fair and thorough review according to the standards outlined in the PFA.

Post-Panel Review

After the in-person meeting, PCORI program staff evaluate final merit review panel 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 the Board. The Selection 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 the Board for consideration and approval.

In addition, PCORI evaluates applicant risk before issuing a PCORI award. Factors considered include financial stability, quality of management systems, audit findings, and past performance on PCORI awards (e.g., compliance with PCORI reporting requirements, conformance to PCORI terms and conditions on previous awards, and timely achievement of milestones). Based on the risk assessment, PCORI may impose special terms and conditions on awardees or withhold contract issuance until such business risks are mitigated. **PCORI will not award new contracts to current awardees with overdue reports (progress, interim, final, etc.) until the overdue reports have been submitted to PCORI.**

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:

- In-person panel discussion notes
- Final average overall score
- Preliminary reviewer critiques
- Application quartile, which provides information for applicants to understand how they did relative to other 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 the PCORI Methodology Standards. Programs also consider the funds allotted for the current funding announcement when deciding which applications to recommend to the Board for approval. Applicants to this current cycle's PFA will receive summary statements in August 2017 and notification of the funding status of their application no later than September 2017.