Treatment of Multiple Sclerosis

Applicant Town Hall

October 11, 2016
Agenda

- Welcome
- Introduction to PCORI
- Background for the PFA
- Programmatic Requirements for this PFA
- Administrative Requirements for this PFA
- Resources
- Questions

Submit questions via the Q&A function in Meeting Bridge.

Ask a question via phone (an operator will standby to take your questions).
Introductions

Diane Bild, MD, MPH
Associate Director
Assessment of Prevention, Diagnosis and Treatment Options

Els Houtsmuller, PhD
Senior Program Officer
Improving Healthcare Systems

Mari Kimura, MS, PhD
Merit Review Officer

Chinenye Anyanwu, PharmD, MPH
Engagement Officer
Engagement

Donna Gentry, MA
Contracts Operations Supervisor
Contracts Management and Administration

PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE
Introduction to PCORI

Diane Bild, MD, MPH
Associate Director
Assessment of Prevention, Diagnosis, and Treatment Options
PCORI

• An independent, non-profit [501-(c)(1)] research institute authorized by Congress in 2010 and governed by a 21-member Board of Governors representing the entire healthcare community
PCORI’s Mission

To help people make informed health care decisions and improve health care delivery and outcomes, by producing and promoting high integrity, evidence-based information that comes from research guided by patients, caregivers and the broader health care community.
PCORI funds comparative effectiveness research

Research that . . .

• Compares benefits and harms of at least two different methods to prevent, diagnose, treat, or monitor a clinical condition or to improve care delivery

• Is performed in real-world populations

• Informs a specific clinical or policy decision

Adapted from Initial National Priorities for Comparative Effectiveness Research, Institute of Medicine of the National Academies
Background for the PFA on Treatment of Multiple Sclerosis

Diane Bild, MD, MPH
Associate Director
Assessment of Prevention, Diagnosis, and Treatment Options
Brief Genesis of this PFA

- Stakeholders proposed this topic to PCORI.
- PCORI held discussions with stakeholders to identify and refine specific comparative effectiveness research questions.
- PCORI issued a targeted PFA on the Treatment of Multiple Sclerosis in fall 2015 and awarded 4 projects in summer 2016:
  - RCT comparing fingolimod and dimethyl fumarate
  - Observational study comparing rituximab with other DMTs
  - RCT comparing three amantadine, modafinil, and methylphenidate for treatment of fatigue in MS
  - RCT comparing clinic-based complementary and alternative medicine vs. home-based CAM via telerehabilitation
- In recognition of the remaining gaps in evidence in the treatment of MS, PCORI re-issued the PFA in October 2016.
Question 1:

- What are the comparative benefits and harms of different disease-modifying therapies (DMTs) or therapeutic strategies in patients with relapsing, remitting multiple sclerosis on symptoms, functioning, quality of life, disease activity, and disease progression?
  - Strategies may include comparisons of initial DMT treatment or comparisons of follow-on treatments in patients for whom initial DMT treatment has failed, including strategies for sequencing or combining agents, changing to a different DMT, or escalating DMT dose.
PFA Questions on Treatment of Multiple Sclerosis

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.
Question 3:

• What is the comparative effectiveness of telerehabilitation vs. conventional direct care interventions for improving outcomes in people with MS, such as functional status, fatigue, and quality of life?
  – Studies should evaluate the effectiveness of telerehabilitation interventions to enhance community-based primary care or neurology practice for patients who do not have access to specialty centers. Applications that employ intervention(s) already in practice are especially attractive.
  – Studies should examine the impact of the telerehabilitation strategies in various subpopulations, including individuals with low socioeconomic status and patients with progressive disease.
Note for this reopened PFA

- The scientific background section and the three priority research questions are the same as in Cycle 3-2015.
- Clarification about payment for costs of system-based interventions is provided.
- Section on Replication and Reproducibility of Research and Data-Sharing requirement has been removed (at the application stage).
- New links to PCORI Policy on Data and Safety Monitoring Plans and on Public Release of Research Findings are included.
- Applicants are advised to review the awards the PCORI has funded on the treatment of multiple sclerosis to ensure that their proposed research complements those projects.
Programmatic Requirements for Letters of Intent and Applications

Els Houtsmuller, PhD
Senior Program Officer
Improving Healthcare Systems
The purpose of the LOI is to identify ideas and proposals that are programmatically responsive and to provide feedback to applicants.

The LOI is 4 pages long, including references.

It is the same as for Cycle 3-2015, except for an additional question about requesting a waiver to cover the costs of the intervention.

The LOIs are reviewed by PCORI staff for each of the items requested in the template.
An important documented decisional dilemma

- Clinical guidelines based on less than optimal evidence
- Credible reviews calling out a research gap, such as systematic reviews
- CER question stated clearly in your Specific Aims
- Proposed comparators should be viable (realistic) and consistent with the decisional dilemma
What PCORI looks for when reviewing LOIs

A well-thought out, appropriate, defensible research strategy

- Adequate study power/appropriate sample size
- Realistic assumptions
- Appropriate study design
- Realistic recruitment strategy, if applicable
Essential characteristics of appropriate studies

- Address at least one of the three priority research questions.
- Include representative patient populations.
- Compare the effectiveness of two or more viable alternative approaches to management of MS.
- Conduct the study 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.
Notes about “usual care”

• “Usual care” is generally not an optimal comparator for CER studies.
  – If the applicant proposes “usual care” as a comparator, it must be well-described and justified as a legitimate comparator (e.g., usual care is guideline-based).
  – A proposal for a usual care comparator must be accompanied by an explanation of how the care given in the usual care group will be measured and how appropriate inferences will be made.
Research activities not supported by this PFA

- Studies of decision aids, including development of decision aids
- Efficacy trials (testing a new intervention)
- Natural history studies
- Clinical prediction tools
- Fundamental science studies
- Evidence syntheses
- Cost-effectiveness studies, including research that aims to compare the overall costs of care between two or more alternatives and use the results to determine the preferred alternative
PCORI Methodology Standards

Methodology Standards: 11 Broad Categories

- Formulating Research Questions
- Patient-Centeredness
- Data Integrity and Rigorous Analyses
- Preventing/Handling Missing Data
- Heterogeneity of Treatment Effects
- Data Networks
- Data Registries
- Adaptive and Bayesian Trial Designs
- Causal Inference
- Studies of Diagnostic Tests
- Systematic Reviews

Patient and Stakeholder Engagement

Chinenye Anyanwu, PharmD, MPH
Engagement Officer
Engagement
Patient-Centeredness vs. Patient and Stakeholder Engagement for the LOI

**Patient-Centeredness**

- Does the LOI mention outcomes (both benefits and harms) important to patients?
- Are the interventions being proposed for comparison available to patients now?

**Patient engagement**

- Does the LOI mention intent to build an interdisciplinary study team that includes appropriate patient and stakeholder representation in consultation with PCORI?
Evidence of appropriate engagement of relevant stakeholders and researchers

• Funding 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.

• Identify the patients and stakeholders you consulted in determining that the proposed study addresses their evidentiary needs for decision-making and indicate your commitment to continuing to engage them actively in the conduct of the study.
Engagement Resources for the Application

– PCORI’s “The Engagement Rubric”

– Sample Engagement Plans

– Compensation Framework

– Engagement Budgeting

– Engagement in Research website page
  http://www.pcori.org/funding-opportunities/what-we-mean-engagement

– PCORI’s Methodology Standards PC-1 to PC-4
Administrative Requirements

Donna Gentry, MA
Contracts Management and Administration
# PFA Budget Limits and Project Duration

## Available Funds and Duration:

Total available: $30 million (direct and indirect costs)

<table>
<thead>
<tr>
<th>Question</th>
<th>Direct costs per project</th>
<th>Duration</th>
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<tbody>
<tr>
<td>1 - DMTs</td>
<td>$10 million</td>
<td>5 years</td>
</tr>
<tr>
<td>2 - non-DMT symptomatic Rx</td>
<td>$3 million</td>
<td>3 years</td>
</tr>
<tr>
<td>3 - telerehabilitation</td>
<td>$5 million</td>
<td>4 years</td>
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</table>
Eligibility to Submit a Letter of Intent

• Any private sector (non-profit or for-profit) research organization

• Any public sector research organization (university or college hospital or healthcare system, laboratory or manufacturer, unit of local, state, or federal government)

• Non-domestic components of organizations based in the US and foreign organizations may apply, as long as there is demonstrable benefit to the US healthcare system and US efforts in the area of patient-centered research can be clearly shown.

• Individuals are not permitted to apply.
Resubmission

- PCORI considers a resubmission to be an application that has completed PCORI’s merit review process and received a summary statement.
- A previous submission in the form of an LOI only (without a full application) is not considered a resubmission.
- If invited to submit an application, applicants are required to include a one-page resubmission letter.
Using the PCORI Online System

• Apply through PCORI Online (https://pcori.fluxx.io)
• Access the website using Chrome or Safari browsers only
• Create a new request and begin the LOI
• Designate the LOI with the following individuals:
  — PI, PI Designee, AO, and Financial Officer
• Enter information into all required fields in the system
• Convert the document to PDF file
• Upload the LOI in the system
• An applicant can save information by clicking the ‘Save and Review’ button.
Complete a Letter of Intent (LOI)

- Refer to the PCORI Online User Manual: Submitting a Letter of Intent
  - PI and Contact Information
  - Project Information
  - Key Personnel
  - Templates and Uploads
- Refer to the PFA-specific LOI Template to address the program’s areas of interest
  - Please make sure to address all required sections of the LOI template
  - Please refer to the specific PFA as each program has its own unique characteristics and requirements
Letter of Intent (LOI) – A Few More Tips

• An LOI is required and must be submitted prior to the deadline. To submit an LOI, download the Letter of Intent Template specifically for the TREATMENT OF MULTIPLE SCLEROSIS Cycle 3 from the Funding Center to begin your LOI.

• You must answer all questions, including the question on brief justification for the cost (“Will not exceed $10 million” is not a sufficient answer!).

• Do not upload additional documents as part of your LOI.

• Letters of endorsements or support are not accepted at this stage.

• Only those LOIs deemed most responsive (programmatically and administratively) to this PFA will be invited to submit a full application.

• Please refer to the PFA, Application Guidelines, and PCORI Online User Manuals in the Funding Center here: http://www.pcori.org/funding-opportunities/announcement/treatment-multiple-sclerosis-cycle-3-2016
Budget Information – Application

• Indirect costs: up to 40%

• Institutional base salary up to $200,000

• Indirect costs are now allowed on the first $25,000 of each subcontractor rather than all subcontractor budgets combined

• The limit for Scientific Travel is $10,000 over the duration of the project, inclusive of the prime and all subcontractors.

• There is no cap on Programmatic Travel but it should be clearly defined and justified as necessary for the success of the project
## Submission and Key Dates

<table>
<thead>
<tr>
<th>What</th>
<th>When</th>
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<tbody>
<tr>
<td>LOI Deadline</td>
<td>November 1, 2016 by 5:00pm ET</td>
</tr>
<tr>
<td>LOI Status Notification</td>
<td>December 2, 2016 by 5:00pm ET</td>
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<tr>
<td>Application Deadline</td>
<td>February 7, 2017</td>
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<td>Merit Review</td>
<td>April 2017</td>
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<tr>
<td>Award Announcement</td>
<td>August 2017</td>
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<tr>
<td>Earliest Start Date</td>
<td>October 2017</td>
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Merit Review

Mari Kimura, PhD
Merit Review Officer
Merit Review

• Multistep process:
  – Full applications screened by PCORI merit review staff for responsiveness to PFA and consistency with LOI
  – Preliminary (online) review
  – In-Person review
  – Post-Panel review (PCORI program staff)

• PCORI guides reviewers to use the bullet points under each merit review criterion to evaluate their assigned applications (see Merit Review section in PFA).
## Merit Review Criteria

### Crosswalk of PCORI Merit Review Criteria with NIH Criteria

<table>
<thead>
<tr>
<th>SIGNIFICANCE</th>
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<tbody>
<tr>
<td>1. Potential for the study to fill critical gaps in evidence</td>
<td></td>
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<tr>
<td>2. Potential for the study findings to be adopted into clinical practice and improve delivery of care</td>
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<tr>
<th>APPROACH</th>
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<tr>
<td>3. Scientific merit (research design, analysis, and outcomes)</td>
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<tr>
<td><strong>NEW</strong> 4. Investigator(s) and environment</td>
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### PCORI-only Merit Review Criteria

<table>
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<tr>
<th>PATIENT-CENTEREDNESS/ENGAGEMENT</th>
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<tbody>
<tr>
<td>5. Patient-centeredness</td>
<td></td>
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<tr>
<td>6. Patient and stakeholder engagement</td>
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</table>
An Inclusive Merit Review

- Invited responsive applications reviewed by panel including 3 reviewer types to bring diverse perspectives.
- Each application reviewed by 3 scientists (including 1 methodologist), 1 patient, and 1 other stakeholder.
Where to go for help

Visit pcori.org/apply
- Application Guidelines
- FAQs
- PCORI Online User Manuals
- Sample Engagement Plans

Schedule a Call with a Program Officer
- Submit a request at pcori.org/content/research-inquiry
- Call 202-627-1884 (programmatic inquiries)
- E-mail sciencequestions@pcori.org

Contact our Helpdesk
- E-mail pfa@pcori.org
- Call 202-627-1885 (administrative and technical inquiries)
Q&A

Ask a question via the Q&A function in Meeting Bridge.

Ask a question via phone (an operator will standby to take your questions).

If we are unable to address your question during this time, e-mail the Helpdesk at pfa@pcori.org.