New Oral Anticoagulants (NOACs) in the Extended Treatment of Venous Thromboembolic Disease

LOI Applicant Town Hall

October 20, 2015
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 chat function in Meeting Bridge.

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

Diane Bild, MD, MPH
Senior Program Officer
Assessment of Prevention, Diagnosis and Treatment Options

Allison Ambrosio, MPH
Program Associate
Assessment of Prevention, Diagnosis and Treatment Options

Suzanne Schrandt, JD
Deputy Director Patient Engagement

Maricon Gardner, CRA
Contracts Associate, Pre-Award Contracts Management and Administration
Introduction to PCORI

Diane Bild, MD, MPH
Senior Program Officer, CER
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

Allison Ambrosio, MPH
Program Associate, CER
Pathway for this Funding Announcement

Stakeholders proposed topic(s) to PCORI and PCORI staff reviewed them

PCORI APDTO Advisory Panel reviewed topic(s)

PCORI engaged stakeholders for workshop discussions, where they recommended topics and priorities (June 9, 2015)

PCORI staff and Science Oversight Committee further refined and approved topics

PCORI Board of Governors reviewed and approved topics for targeted PFA (August 18, 2015)
Oral anticoagulants are used in several serious health conditions

• Prior to 2010, virtually the only anticoagulant used was warfarin
• Within the past 5 years, four new oral anticoagulants (NOACs) account for 62% of new prescriptions and 98% of anticoagulant-related drug costs
• The four NOACs include dabigatran, rivoroxaban, apixaban, and edoxaban

NOACs are considered to have several advantages:

• Fixed, once- or twice-a day dosing
• Lack of requirement for blood monitoring
• Lower risk of intracranial hemorrhage
Need for CER for Extended Treatment of Venous Thromboembolic Disease with NOACs

Data are lacking to guide clinical practice:

• DVT or PE recurrence occurs in 17.5% at 2 years and 24.6% at 5 years
  – Extending anticoagulation beyond the recommended treatment of 3-6 months is associated with a reduction in the risk of recurrence
  – Management of recurrent DVT and PE is also associated with increased bleeding
• There have been no studies comparing NOACs for extended treatment of DVT or PE
Available Funds and Duration:

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

- Direct Costs: $10 million/project
- Duration: Maximum 5 Years
Programmatic Requirements

Diane Bild, MD, MPH
Senior Program Officer, CER
Overview of LOI Purpose and Process

• To identify ideas and proposals that are programmatically responsive
• To provide feedback to applicants

• Letters of Intent are reviewed by PCORI staff for each of the items requested.
• A decision and feedback is provided by December 18, 2015.
LETTER OF INTENT (LOI) TEMPLATE: New Oral Anti-Coagulants (NOACs) in the Extended Treatment of Venous Thromboembolic Disease

Instructions:

Please provide the information requested on the attached template. You must answer all questions listed in the template. Highlight changes if this is a resubmission. Aside from removal of the questions under each section header, no other modifications may be made to this template; any modifications will result in administrative withdrawal of the LOI. Applicants are required to follow the rules and guidelines listed below:

1. Replace the questions on the next page with your response, but retain the question numbers.
2. Do not include figures or general tables. Tables can only be included for power calculations.
3. References should be listed at the end and are not included in the four-page limit.
4. Do not upload this cover page.
5. Do not include supplemental materials (e.g., supporting journal articles, Letters of Support).

Formatting Guidelines:

- **Font:** Calibri size 11, figures and captions may have size 8 font
- **Spacing:** Single
- **Margins:** Half-inch (The header may fall within the top margin, but the body text should not begin closer than a half-inch from the edge of the page.)
- **Page limit:** Four pages
LETTER OF INTENT (LOI) TEMPLATE: NEW ORAL ANTI-COAGULANTS

TITLE OF PROPOSED STUDY

RELEVANCE OF THE RESEARCH QUESTION TO CURRENT TREATMENT DECISION

1. What is the precise question or clinical dilemma in decision making that your research is designed to address?

2. Describe how your comparative effectiveness research (CER) question aims to address documented or known evidence gaps. Provide references for these known gaps from systematic reviews and clinical practice guidelines. Describe how the proposed study will help address decisional uncertainty currently facing patients and clinicians or other decision makers.

OBJECTIVES

3. What are the specific aims of the study?

METHODS

4. Describe:
   a) Study design
   b) Study population and proposed inclusion and exclusion criteria, identify clinical subgroups as appropriate.
   c) Comparators (the two or more options being compared): Provide details about each of the comparators and how you plan to measure their use and implementation within the study. Since “usual care” is often highly variable, it makes for a poor comparator for discerning differences between interventions. If the known evidence gap dictates the comparison to “usual care”, then describe how you will assess the fidelity and variability of that “usual care” in the individual patients participating in your study.
   d) Study outcomes, including measures important to patients and families
   e) Data sources and resources, if the study involves substantial use of existing and secondary data
Question:

• How do different strategies for extended anticoagulation treatment compare for patients who have completed a course of treatment after an initial episode of DVT or PE?
  – Subgroups of particular interest include elderly and patients with chronic renal function
  – 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
Essential characteristics of studies

- Address the priority research question
- Include representative patient populations
- Have strong endorsement and participation by relevant patient, professional, payer, and/or purchaser organizations
- Take place within the community outpatient setting
- 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 (treatment heterogeneity)
- Compare the effectiveness of two or more alternative approaches to extended treatment with NOACs for improving patient-centered outcomes
Pragmatic vs. explanatory trials

- PCORI aims to produce evidence that can be easily applied in real-world settings and focuses on existing clinical interventions.
- Studies should be on the pragmatic end of the spectrum.

Notes about “usual care”

- “Usual care” is generally not an optimal comparator for CER studies.
  - It is ill-defined, difficult to quantify, and subject to considerable geographic and temporal variations, thus limiting interpretability, applicability, and reproducibility.
  - If the applicant proposes “usual care” as a comparator, it must be 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

• Efficacy trials (testing a new intervention)
• 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
• Natural history studies
• Instrument development, pharmacodynamics, and fundamental science or study of biological mechanisms
• Studies of decision aids, including development of decision aids
• Clinical prediction tools
PCORI Methodology Standards

Not to be addressed, per se, in LOI, but be aware and prepared!

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

Examples of Methodology Standards:

- RQ-2 Develop a formal study protocol
- RQ-4 Identify and assess participant subgroups
- HT-3 All HTE (heterogeneity of treatment effects) claims must be based on appropriate statistical contrasts among groups being compared, such as interaction tests or estimates of differences in treatment effect
- MD-1 Describe methods to prevent and monitor missing data

The Methodology Standards do not address all issues related to study designs and methods and are considered minimal.
What PCORI looks for when reviewing LOIs

An important documented decisional dilemma

- Clinical guidelines based on less than optimal evidence
- Credible reviews calling out a research gap, such as a systematic review
- CER question stated in your Specific Aims
- Proposed comparators should be viable (realistic) and consistent with the decisional dilemma
A clear statement of the CER question

• Typical wording:

“What are the comparative benefits and harms of __________ vs. __________ for patients undergoing extended treatment for Venous Thromboembolic disease?”

• Note: There can be more than two clinical options.

TIP: If you are unable to articulate and support a clear, compelling CER question or decisional dilemma, you may want to re-think your decision to submit an LOI to PCORI.
A well-thought out, appropriate, defensible research strategy

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

Note: The LOI is only 4 pages, so there is not room for much detail, but poor methodology is a frequent reason for LOI rejection.

**TIP:** Work with a biostatistician on the study design.
Responsiveness Review

• Letters of Intent are reviewed based on criteria detailed in each PFA
• Additional screening for
  – Comparative effectiveness research
  – NON Inclusion of cost-effectiveness analysis
  – Administrative Guidelines
• Only responsive LOIs will be invited to submit a full application
Patient and Stakeholder Engagement

Suzanne Schrandt, JD
Deputy Director, Patient Engagement
Patient-Centeredness vs. Patient Engagement

- **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 and Stakeholder 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.

What PCORI looks for when reviewing LOIs
Several approaches to engagement can succeed. PCORI provides many engagement resources for applicants:

- PCORI’s “The Engagement Rubric”

- Sample Engagement Plans

- Engagement in Research website page
  [http://www.pcori.org/funding-opportunities/what-we-mean-engagement](http://www.pcori.org/funding-opportunities/what-we-mean-engagement)

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

Mary Gardner, CRA
Contracts Associate, Pre-Award
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.
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
  - Pre-Screen Questionnaire
  - 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)

- 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 New Oral Anticoagulants (NOACs) in the Extended Treatment of Venous Thromboembolic Disease - 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/new-oral-anticoagulants-noacs-extended-treatment-venous
NOACs tPFA LOI requirements

- Four page limit – See requirements for font size and type, margins, and line spacing.
- References should be listed at the end and are not included in the four-page limit
- LOIs that exceed four pages will not be reviewed.
Formatting

- Include the Principal Investigator’s (PI’s) full name on every page in the top left corner of the page header.
- Use at least half-inch margins and single spacing.
- Use size 11 Calibri for the main body of the text. Figures and captions may have smaller type.
- Each page must be numbered consecutively for each PDF upload.
- Keep the numbering of the LOI questions within the LOI template.
- Save the document as, Principal Investigator (PI) Last Name_(last five digits of Request ID)_LOI.pdf. A request ID number will be automatically generated once the LOI has been saved.
Budget Information

- Indirect costs: up to 40%
- Institutional base salary up to $200,000
- Indirect costs are capped on subcontracts / sub awards
- The limit for Scientific Travel is $10,000 over the duration of the project. There is no cap on Programmatic Travel
## Submission and Key Dates

<table>
<thead>
<tr>
<th>What</th>
<th>When</th>
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<tbody>
<tr>
<td>LOI due in PCORI Online</td>
<td>November 12, 2015 by 5:00pm ET</td>
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<tr>
<td>Applicants notified as to whether they have been selected to submit a full application</td>
<td>December 18, 2015 by 5:00pm ET</td>
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<td>Earliest Start Date</td>
<td>September 2016</td>
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Resources
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 chat 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.