



## **Cycle 3 2015 Funding Cycle**

PCORI Funding Announcement:

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

Published October 12, 2015

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This PCORI Funding Announcement applies to the funding cycle that closes on February 16, 2016 at 5 p.m. (ET). Application guidelines, templates, and other resources are available at <http://www.pcori.org/2015-Cycle-3-New-Oral-Anticoagulants>.



## **About PCORI**

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

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

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## Overview

Published	October 12, 2015
Letter of Intent Due	November 12, by 5 p.m. (ET)  Letters of Intent (LOIs) will be screened for responsiveness to this PCORI Funding Announcement (PFA) and fit to program goals. Only those applicants selected will be permitted to submit full applications. Notification of denial or approval to submit a full application will occur no later than December 18, 2015.
Summary	<p>The Patient-Centered Outcomes Research Institute (PCORI) seeks to fund randomized clinical trials (RCTs) or observational studies that compare two or more alternatives for addressing management of deep vein thrombosis (DVT) or pulmonary embolism (PE) with extended anticoagulation treatment. The research is expected to examine how different strategies for extended anticoagulation treatment compare for patients who have completed a course of anticoagulation treatment for an initial episode of DVT or PE. The setting would be a community outpatient center.</p> <p>Proposed studies must address clinical and healthcare delivery choices faced by patients, their caregivers, clinicians, and delivery systems. In addition, these proposed studies must compare two or more active interventions. They must involve patient populations that are representative of the US population, and they must be large enough to provide precise estimates of hypothesized effectiveness differences and support evaluation of potential differences in treatment effectiveness in patient subgroups.</p> <p>For this solicitation, PCORI is not requiring that relevant national patient organizations, professional organizations, and payer or purchaser organizations be formally included as partners and active participants prior to contract award. However, applicants should document that they have consulted with patients and other stakeholders to identify the important decisional dilemmas and evidence needs that will drive development of the research questions or reference previously documented decisional dilemmas. Successful applicants are required to work in collaboration with PCORI staff upon award of the proposed studies to establish a project Study Advisory Committee (SAC) (or other appropriate engagement body, see the <a href="#">NOACs FAQs</a>) that is comprised of national or regional organizations that represent, at a minimum, patients and families with lived experience, relevant clinicians, payers, and health plans. Other representation may be recommended in collaboration with PCORI, including individual patients with lived experience and other relevant stakeholders, including scientific and methodological experts. The SAC serves to advise and assist the research team with further refinement of the study questions, outcomes, and protocol. PCORI expects most applications to propose study designs that use randomization, either of individual participants or clusters, to avoid bias due to confounding. However, we encourage investigators who identify exceptional opportunities, by virtue of natural experiments and the existence of large registries, to use observational designs to address the research questions. <b>Note that this funding program does not support applications to conduct cost-effectiveness analysis, systematic reviews, or development or evaluations of shared decision making or decision-support tools.</b></p>
Applicant Resources	See <a href="http://www.pcori.org/2015-Cycle-3-New-Oral-Anticoagulants">http://www.pcori.org/2015-Cycle-3-New-Oral-Anticoagulants</a>



Key Dates	<p>Online System Opens: October 12, 2015</p> <p>Applicant Town Hall Session: Letter of Intent (LOI) Deadline: Screening Notification: October 20, 2015, 1 p.m. – 2:30 p.m. (ET) November 12, 2015, by 5 p.m. (ET) December 18, 2015</p> <p>Application Deadline: February 16, 2016, by 5 p.m. (ET)</p> <p>Merit Review Dates: May 2016</p> <p>Awards Announced: July 2016</p> <p>Earliest Project Start Date: September 2016</p>
Maximum Project Budget (Total Direct Costs)	\$10 million
Maximum Research Project Period	5 years
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, laboratory, or manufacturer; or unit of local, state, or federal government. All U.S. applicant organizations must be recognized by the Internal Revenue Service. Nondomestic components of organizations based in the United States and foreign organizations may apply as long as there is demonstrable benefit to the U.S. healthcare system and U.S. efforts in the area of patient-centered research can be clearly shown. Organizations may submit multiple applications for funding. Individuals are not permitted to apply.</p>
Review Criteria	<ol style="list-style-type: none"> <li>1. Potential for the study to fill critical gaps and generate actionable evidence</li> <li>2. Potential for the study findings to be adopted into clinical practice and improve delivery of care</li> <li>3. Scientific merit (research design, analysis, and outcomes)</li> <li>4. Patient-centeredness</li> <li>5. Patient and stakeholder engagement</li> </ol>
Contact Us	<p><b>Programmatic Inquiries:</b> Contact the PCORI Helpdesk via email (<a href="mailto:sciencequestions@pcori.org">sciencequestions@pcori.org</a>), phone (202-627-1884), or complete the Research Inquiry Form (<a href="http://www.pcori.org/content/research-inquiry">http://www.pcori.org/content/research-inquiry</a>). PCORI will provide a response within three business days. However, we cannot guarantee that all questions will be addressed in a timely fashion when the inquiry is made three or fewer business days prior to an LOI or application deadline.</p> <p><b>Administrative, Financial, or Technical Inquiries:</b> Contact the PCORI Helpdesk at <a href="mailto:pfa@pcori.org">pfa@pcori.org</a>. 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 prior to 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	Deadlines are at 5 p.m. (ET). If deadlines fall on a weekend or a federal holiday, the deadline will be the following Monday or the next day after the federal holiday.



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## I. Introduction

### Summary of Program

The Patient-Centered Outcomes Research Institute (PCORI) is launching this funding initiative to support patient-centered comparative clinical effectiveness research (CER) that addresses important questions about the extended treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE) with oral anticoagulants after the patient has completed an initial course of guideline-based anticoagulation treatment. Through this PCORI Funding Announcement (PFA), PCORI seeks to fund randomized clinical trials (RCTs) or comparative observational studies with sufficient sample size to address the research question and to generate information that is readily generalizable to the broader population.

Competitive applications must address the priority research question described in this funding announcement. Additionally, applications should:

- Include patients who are representative of those with a history of treated DVT or PE
- Have strong endorsement and study participation by relevant patient organizations, professional organizations, and payer 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, such as racial and ethnic minority populations and individuals with low socioeconomic status
- Describe, to the extent possible, what can be learned about the natural history of disease and treatment heterogeneity
- Compare the effectiveness<sup>1</sup> of two or more alternatives for improving patient-centered outcomes

### Background

Oral anticoagulants are used in several serious health conditions, including atrial fibrillation, DVT, and PE, as a means to prevent stroke and further thrombosis and PE, as well as to prevent postoperative DVT, particularly after hip and knee surgery.<sup>2</sup> Prior to 2010, virtually the only oral anticoagulant used was the vitamin K antagonist warfarin; however, within the past five years, four new oral anticoagulants (NOAC), also referred to as direct thrombin inhibitors or direct factor Xa inhibitors, now account for 62

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<sup>1</sup> 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 [ec.europa.eu/enterprise/sectors/healthcare/files/docs/rea\\_principles\\_en.pdf](http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/rea_principles_en.pdf)).

<sup>2</sup> US Food and Drug Administration. 2012. FDA Drug Safety Communication: Pradaxa (dabigatran etexilate mesylate) should not be used in patients with mechanical prosthetic heart valves [Press Release]. <http://www.fda.gov/Drugs/DrugSafety/ucm332912.htm/>.

percent of new prescriptions and 98 percent of anticoagulant-related drug costs.<sup>3</sup> The four NOACs include dabigatran—an oral thrombin inhibitor—and rivaroxaban, apixaban, and edoxaban, which are oral factor Xa inhibitors.<sup>4</sup>

While warfarin is still in wide use, NOACs are considered to have several advantages, including fixed, once- or twice-a-day dosing, lack of a requirement for blood monitoring, and lower risk of intracranial hemorrhage than warfarin.<sup>5</sup>

The annual incidence of DVT or PE is one to two per 1,000 population, and 10–30 percent die within one month of diagnosis.<sup>6</sup> After an initial event, DVT or PE recurrence occurs in 17.5 percent at two years and 24.6 percent at five years.<sup>7</sup> Extending anticoagulation beyond the recommended treatment of three to six months is associated with a reduction in the risk of recurrence as long as treatment is continued, but is also associated with increased bleeding.<sup>8,9</sup> Data are lacking to guide clinical practice, and there have been no studies comparing NOACs for extended treatment of DVT or PE. Clinical decision making is particularly difficult in elderly patients and those with renal dysfunction, in whom data are particularly sparse and because NOACs are at least partially excreted by the kidney, particularly dabigatran, in which renal clearance is 80 percent.

### Research Topic Prioritization

PCORI relies on input from multiple stakeholders to set its research priorities. Members of its advisory panels include patients, clinicians, researchers, purchasers, payers, industry, and other healthcare stakeholders. Many stakeholders have asked PCORI to consider funding research on the extended use of anticoagulation treatment for patients who have completed a course of treatment after an initial episode of DVT or PE. PCORI's Advisory Panel on Assessment of Prevention, Diagnosis, and Treatment Options then ranked as a high-priority topic when it met on April 9, 2015. PCORI convened a large multi-stakeholder workshop on June 9, 2015 to provide further input on whether specific NOAC-related CER questions could be addressed by PCORI-funded research. More than 30 invited stakeholders attended in person. The meeting was open to the public via teleconference and webinar.

Before the workshop, PCORI asked invited participants to propose specific CER questions about NOACs.

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<sup>3</sup> Desai, NR, Krumme, AA, Schneeweiss, S, et al. Patterns of initiation of oral anticoagulants in patients with atrial fibrillation: quality and cost implications. *Am J Med*, 2014, 4(4): 314–23.

<sup>4</sup> Yeh, CH, Gross, PL, Weitz, JI. Evolving use of new oral anticoagulants for treatment of venous thromboembolism. *Blood* 2014; 124:1020–8. All four agents have been compared with conventional anticoagulant therapy for the treatment of acute symptomatic VTE, and all but edoxaban have been compared with a placebo for extended treatment.

<sup>5</sup> Lip, GY, Lane, DA. Stroke prevention in atrial fibrillation: a systematic review. *JAMA* 2015; 313:1950–62.

<sup>6</sup> White, RH. Four Topics in venous thromboembolism: The epidemiology of venous thromboembolism. *Circulation*. 2003; 107:14–18.

<sup>7</sup> Barnes, GD, Kanthi, Y, Froehlich, JB. Venous thromboembolism: Predicting recurrence and the need for extended anticoagulation. *Vascular Medicine* 2015; 20:143–152.

<sup>8</sup> Schulman, S, Kearon, C, Kakkar, AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *NEJM* 2013; 368:709–18.

<sup>9</sup> Kearon, C, Akl, EA, Comerota, AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9<sup>th</sup> ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141:e419S–94S.

PCORI staff grouped the questions into four categories: medication adherence, dosing strategies, comparative benefits and harms among the NOACs, and comparative benefits and harms of NOACs versus warfarin. These questions were discussed, revised, and ranked by the participants during breakout sessions at the workshop.

After the workshop, PCORI staff and its Science Oversight Committee reviewed and refined the questions. One question, on the comparative effectiveness of different oral anticoagulants, including NOACs, for extended treatment of DVT or PE was reviewed and approved by PCORI's Board of Governors on August 18, 2015 as the basis for this targeted funding announcement.

### Priority Research Questions

Applications should propose RCTs or comparative observational studies that address the following priority research question. PCORI particularly encourages pragmatic trial designs. Pragmatic trials are designed to maximize applicability of the study's results in routine clinical practice. They tend to be conducted in routine clinical care settings, and in many cases they must be relatively large, in part to be able to demonstrate differences in comparative effectiveness between different patient subgroups. They should impose fewer constraints on usual practice than traditional RCTs. The protocols for these trials are typically less complex than efficacy studies.<sup>10,11</sup>

Observational studies are appropriate when randomization is not feasible, and when rich, population-based clinical data can be obtained in whole or in part from existing databases. 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 explain carefully how such bias will be minimized and evaluated.

The priority research question is:

- 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 dysfunction.

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.

### Funds Available

PCORI has devoted up to \$30 million in total costs under this PFA to fund high-impact studies on the comparative effectiveness of different anticoagulants for extended anticoagulation treatment in patients who have completed a course of treatment after an initial episode of DVT or PE. The proposed budget for individual studies may range up to \$10 million in total direct costs as appropriate, depending

<sup>10</sup> Patsopoulos, NA. A pragmatic view on pragmatic trials. *Dialogues Clin Neurosci*. 2011; 13:217–24. <http://ncbi.nlm.nih.gov/pmc/articles/PMC3181997/>.

<sup>11</sup> Thorpe, KE, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *CMAJ*. 2009; 180:E47–57. <http://cmaj.ca/content/180/10/E47.full.pdf/>.

on the specific priority research question or questions the study proposes to address. The maximum project period is five years.

In all cases, PCORI will expect that, in preparing applications, researchers have partnered extensively with relevant patient organizations, specialty professional organizations, healthcare systems, insurers, and/or employer purchasers. Involvement of these organizations in finalizing and endorsing the research question and their participation in conducting the proposed study are essential requirements for labeling a research question as high priority. If one or more key stakeholders has or have declined to endorse the study, the reason(s) should be explained clearly in the application.

Given the significant treatment costs associated with many of the newly available therapies, 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 drugs and non-study protocol-related clinical costs and services rendered in the care processes. Because high levels of out-of-pocket costs would be likely to drive down the use of newer therapies, investigators must also explain how this would be handled. Of particular concern would be different levels of co-payment between two arms in a comparative study. Ideally, cost-sharing barriers will be eliminated in the study arms or equalized. If the study design does not allow for either option, the applicant should explain why and should also discuss how differences in co-payment costs will be accounted for in the study analysis.

It is expected that project budgets and duration will vary substantially, depending on the topic and approach selected, needs for recruitment and/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, and the supportive involvement of delivery systems or health plans to enhance recruitment, data collection, and coverage of treatment-related costs. A prolonged recruitment period is not an acceptable rationale for longer studies.

## II. Guidance for Preparing Applications

### Specific Requirements

The proposed study should strive to meet all of the following requirements:

- Focus on a comparative effectiveness question that is important to patients and other decision makers
- Address a research gap that has either been substantiated by an existing (recent or updated) rigorously conducted systematic review or specifically 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, in order 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 and

purchaser consortia, and/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 or for clear demonstration of noninferiority; in addition, the sample size must support testing of a priori hypotheses related to potential differences in effectiveness in relevant patient subgroups (heterogeneity of treatment effect [HTE])
- Examine diverse populations receiving care in real-world settings
- Have strong interest from and support by host delivery systems and clinical care settings
- Specify broad and simple eligibility criteria that will allow wide generalization of results, while attending appropriately to any ethical concerns of excess risk in some patient subgroups
- Compare interventions that are known to be efficacious, effective, or commonly in use, and can be implemented in real-world settings
- Include PROs as a primary outcome, when appropriate
- Provide preliminary evidence of the potential for efficient recruitment, high participation rates, and appropriate oversight by local or centralized Institutional Review Boards (IRBs), including plans for streamlining or waiving individual informed consent in cases of low-risk interventions. PCORI believes that the intensity of oversight and the complexity of informed consent procedures should be closely related to the degree of risk from study participation. Applicants must address this issue and should present evidence that the study will not encounter significant barriers to recruitment or participation
- Adhere to all applicable [PCORI Methodology Standards](#)<sup>12</sup>
- In the case of randomized trials, also adhere to current best practices (standardized inclusion and exclusion criteria; proper randomization; techniques to minimize potential for missing data; appropriate safety monitoring, including establishment of a data and safety monitoring board [DSMB] or indication of why such a board is unnecessary)
- Include a plan for sharing, de-identified data for access by other researchers following completion of the study

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

- Consult with patients and other stakeholders on their decisional dilemma and evidence needs or reference previously documented decisional dilemmas in preparation for the

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<sup>12</sup> Available at <http://www.pcori.org/research-results/research-methodology/>.

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

### Nonresponsiveness

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

- Tests efficacy (or comparative efficacy) within a tightly protocol-controlled research setting (as opposed to more real-world, pragmatic CER)
- Conducts a formal cost-effectiveness analysis
- Directly compares the costs of care between two or more alternative approaches to providing care
- Conducts studies of the natural history of disease, instrument development, pharmacodynamics, and fundamental science or study of biological mechanisms
- Evaluates new or existing decision support tools; this includes the development and evaluation of a decision support or shared decision tool or system for patients, clinicians, or both patients and clinicians
- Develops clinical prediction or prognostication tools

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

PCORI does have an interest, however, in studies that address questions about conditions that lead to

high costs to the individual or to society. This is included in our review criterion on impact of the condition on the health of individuals and populations. Thus, PCORI is interested in studies that:

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

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

Furthermore, PCORI discourages proposals in the following categories and is likely to deem them nonresponsive:

- Study of the natural history of disease
- Instrument development
- Pharmacodynamics
- Fundamental science or study of biological mechanisms
- Establishing efficacy for a new clinical strategy
- Pilot studies intended to inform larger efforts
- Comparisons of patient characteristics rather than clinical strategy options

### Features of Patient-Centered Outcomes Research (PCOR)

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

- Assesses the benefits and harms of preventive, diagnostic, therapeutic, or palliative care in informing decision making, highlighting the choices that matter to people
- Is inclusive of an individual's preferences, autonomy, and needs, focusing on outcomes that people notice and care about, such as survival, functioning, symptoms, and health-related quality of life
- Incorporates a wide variety of settings and diversity of participants to address individual differences and barriers to implementation and dissemination
- Directly compares clinical interventions that are generally available in clinical settings
- Obtains the perspectives of stakeholders to address the burdens to individuals, availability of services, and requirements for technology and personnel

### Leveraging Existing Resources

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

### Preliminary Data and Use of Accepted Measures

PCORI encourages investigators to design their research using valid patient-centered outcomes measures and include preliminary data that supports the use of the proposed measures in the study population. Investigators are encouraged to consider those measures described in the *Patient Reported Outcomes Measurement Information System (PROMIS)*.<sup>13</sup>

### Methodological Considerations

Regardless of study design, proposals must adhere to all relevant *PCORI Methodology Standards*.<sup>14</sup> These include 47 individual standards that fall into 11 categories. The first five categories are cross-cutting and are relevant to most PCOR studies. Researchers should refer to all of these standards when planning and conducting their research projects. These five categories are:

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

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

- Standards for Data Registries
- Standards for Data Networks as Research-facilitating Infrastructures
- Standards for Causal Inference Methods
- Standards for Adaptive and Bayesian Trial Designs
- Standards for Studies of Diagnostic Tests
- Standards for Systematic Reviews

Most of these standards should be considered “minimal” standards. Additional best practices, including relevant guidelines for the conduct of clinical trials developed by other organizations, should be addressed in the application for PCORI funding. To help reviewers quickly identify the adherence to a particular standard, applicants must cite each methodology standard within their proposals as the

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<sup>13</sup> Available at <http://nihpromis.org/>.

<sup>14</sup> Available at <http://pcori.org/research-we-support/the-pcori-methodology-report/>.

standard is being addressed. For example, when applicants describe the need for their proposed study within the Background section, they should indicate the particular standard for Identifying Gaps in Evidence in parentheses, such as “(RQ-1).”

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

### **Clinical Trial Design Guidance and Consultation**

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

### **Patient and Stakeholder Engagement**

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

PCORI has developed the [Engagement Rubric](#)<sup>15</sup> to guide the integration of patients and other stakeholders in the development, oversight, management, and implementation of research studies. Additionally, studies are expected to adhere to PCORI’s [Methodology Standards](#) associated with patient-centeredness and to the PCOR Engagement Principles found within the rubric. PCORI also has a [compensation framework](#)<sup>16</sup> for guidance on compensating individual patient partners on the research team. These and additional resources are available in [PCORI’s Funding Center](#).

PCORI understands that applicants may not have the resources to establish formal partnerships prior to

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<sup>15</sup> Available at <http://www.pcori.org/sites/default/files/Engagement-Rubric.pdf>.

<sup>16</sup> Available at <http://www.pcori.org/sites/default/files/PCORI-Compensation-Framework-for-Engaged-Research-Partners.pdf>.

contract award, but expects applicants to discuss in their application their plan to work with PCORI to create the types of partnerships with national and regional patient and other stakeholder groups that will contribute to refinement of research questions, outcomes, protocols, and study conduct and dissemination.

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

### Populations Studied

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

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

### Budget and Duration of Project

Applicants may request up to \$10 million in total direct costs for a research project period not to exceed five years (not including peer review). The maximum budget includes all research *and* peer-review-related costs (please refer to the Application Guidelines for further details). Note that PCORI will not cover costs for interventions that are being compared in the proposed study (see Appendix 2 in the [Application Guidelines](#) for details). Applicants should submit realistic budgets and timelines. For those rare circumstances in which the estimated total direct costs exceed \$10 million, provide in your LOI a detailed justification that ties the extra expense to the success of the project. Not all requests for additional funds will be approved. Any request for a research project period longer than five years will be denied. For further information regarding PCORI's policies about allowable and unallowable costs, refer to Appendix 2 of the Application Guidelines.

The funding mechanism for this program is a contract. Total project funding is contingent upon successful programmatic and budget performance (e.g., meeting recruitment targets). Milestones and targets, as well as possible pilot phases for the sole purpose of assessing feasibility of recruitment, should be included in the budget and will be negotiated at the time of the award. Awardees will be expected to provide corroborating evidence to receive continual funding support. Some of the activities that will be considered during negotiations and subsequently include:

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



Refer to the [Application Guidelines](#)<sup>17</sup> 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 research. PCORI follows the Federal Policy for the Protection of Human Subjects (45 CFR part 46), including the Common Rule. For more detailed information, see Section 5 “Human Subjects Research Policy” from the [Supplemental Grant Application Instructions for All Competing Applications and Progress Reports](#),<sup>18</sup> issued by the US Department of Health and Human Services (HHS). PCORI does not require that applicants comply with sections of this policy that refer to requirements for federal-wide assurance (FWA), or that refer to standards for inclusion of women, minorities, and children. PCORI requires applicants proposing clinical trials to consider including a data- and safety-monitoring plan. Awardees must also comply with appropriate state, local, and institutional regulations and guidelines pertaining to the use of human subjects in research.

PCORI merit reviewers will examine plans for protection of human subjects in all applications and may provide comments regarding the plans (see [How to Evaluate Human Subjects Protections](#)<sup>19</sup>). Reviewers’ comments on human subjects research are not reflected in the overall application score, but may be used by PCORI staff during any potential funding negotiations. Final determinations about adequacy of human subjects protections rest with the IRB or IRBs that have jurisdiction for the study.

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

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

PCORI requires all applicants to adhere to the National Institutes of Health (NIH) policy on education in the protection of human subject participants in the conduct of research. This applies to all personnel listed as Key Personnel in the application. The policy and FAQs are available [from the NIH website](#).<sup>20</sup>

### **Replication and Reproducibility of Research and Data-Sharing Plan**

PCORI is committed to maximizing the utility and usability of data collected in our funded projects. This is essential to building confidence in the accuracy of these findings. PCORI supports policies to promote sharing of study documentation (e.g., study protocol, programming code, and data definitions) so that

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<sup>17</sup> Available at <http://www.pcori.org/sites/default/files/PCORI-PFA-2015-Cycle-3-Targeted-Application-Guidelines.pdf>.

<sup>18</sup> See <http://grants.nih.gov/grants/funding/424/supplementalinstructions.docx>.

<sup>19</sup> See <http://www.pcori.org/sites/default/files/PCORI-Checklist-for-Evaluating-Human-Subjects-Protections.pdf/>.

<sup>20</sup> See <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-054.html/>.

other researchers may replicate the findings in other populations. Propose a method for sharing data and appropriate documentation upon request.

### Peer Review and Release of Research Findings

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

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

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

## III. How To Submit an Application

### Letter of Intent

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

Answer all of the questions in the LOI template. This includes the question on brief justification for the proposed cost of the study; providing an answer "the cost not to exceed \$10 million" is not sufficient. Then upload your document to the PCORI Online System. The deadline for LOI submission is November 12, 2015, by 5 p.m. (ET).

### Letter of Intent Review

LOIs are evaluated on the following criteria:

- Whether the proposed topic addresses the high-priority research questions identified in this

funding announcement

- Importance of the specific research question (comparison), as evidenced by critical gaps identified by clinical guidelines developers and/or recent relevant systematic reviews
- A sufficient size or scope that the proposed topic will have a significant impact on patient outcomes and healthcare practices
- Clarity and credibility of applicants' responses to the LOI questions, as well as their justification of the proposed size of the study citing published estimates, including effect sizes, standard deviations, and need for rigorous comparative analysis of important subgroups
- Prior relevant experience
- Programmatic fit and balance, taking into consideration whether the research study question and study design are compliant with requirements in this funding announcement
- 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. LOIs are reviewed by a minimum of two PCORI staff and are not scored during review. Notification of denial or approval to submit an application will occur no later than December 18, 2015. Please refer to the [Application Guidelines](#) for information on how to submit your LOI via PCORI Online.

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

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

If you need to change any of this information or have any questions, email [pfa@pcori.org](mailto:pfa@pcori.org).

**Note:** A PI may submit multiple LOIs in a cycle but the research topics/projects should not be similar. If a PI submits an LOI to multiple PFAs, LOIs that show scientific overlap or that appear to be duplicate submissions will be disqualified. PCORI will contact the PI and give them an opportunity to choose which PFA they would like to apply to. An individual listed as a PI on one LOI may be listed and serve in another role (e.g., co-investigator, co-PI) on other LOIs within the same PFA during the same cycle.

### **Submission Dates**

LOIs and applications must be submitted in accordance with the published dates and times listed in the



overview of this PFA and in the [PCORI Funding Center](#).<sup>21</sup>

### PCORI Online

To submit a proposal, you must register with [PCORI Online](#)<sup>22</sup> and submit both an LOI and an application for each cycle in which you are applying.

### Applicant Resources

<b>PCORI Funding Center</b>	<a href="http://www.pcori.org/2015-Cycle-3-New-Oral-Anticoagulants">http://www.pcori.org/2015-Cycle-3-New-Oral-Anticoagulants</a>
<b>PCORI Online System</b>	<a href="http://pcori.fluxx.io">pcori.fluxx.io</a>
<b>PCORI Funding Awards</b>	<a href="http://pcori.org/pfaawards">pcori.org/pfaawards</a>

## IV. Merit Review

PCORI merit review is a multiphase process that includes:

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

### Application Review Criteria

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

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

The proposal should address the following questions:

- Does the application convincingly describe clinical burden?
- Does the application identify a critical gap in current knowledge as noted in systematic reviews, guideline development efforts, or previous research prioritizations?

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<sup>21</sup> Available at <http://www.pcori.org/funding-opportunities/>.

<sup>22</sup> Available at <https://pcori.fluxx.io/>.

- Does the study identify variations in practice patterns that suggest clinical uncertainty?
- Does the application describe the decisional dilemmas experienced by patients and other stakeholders that this study would address?
- Does the study or application have the potential to fill these evidence gaps and inform decision making for key stakeholders (provide example)?

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

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

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

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

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

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

intervention and the research design (e.g., cluster randomized design)?

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

#### **Criterion 4. Patient-centeredness**

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

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

#### **Criterion 5. Patient and stakeholder engagement**

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

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

communications at other times. These are to be budgeted activities and represented in the project milestones. The proposal should address the following:

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

### Preliminary Review

PCORI conducts rigorous merit review of the full applications it receives. Applications may be eliminated from the review process for administrative or programmatic reasons (i.e., nonresponsiveness). An application may be eliminated if it is incomplete or submitted past the stated due date and time, or if it does not meet the administrative or formatting criteria outlined in the Application Guidelines, in the PCORI templates, and in [PCORI Online](#).<sup>23</sup> It may also be withdrawn if it is not responsive to the guidelines described in this PFA, describes research that is not comparative, includes cost-effectiveness analysis, or otherwise fails to meet PCORI programmatic requirements. Per our authorizing legislation, if two proposed research plans overlap, funding preference must be given to applications submitted on behalf of NIH and the Agency for Healthcare Research and Quality (AHRQ).

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

### In-Person Review

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

During the in-person review, panels meet to discuss applications and to clarify further the merits of the proposed research, as well as to identify areas for improvement. Additionally, each application is re-scored based on the content of discussion. The chair and PCORI MRO lead the in-person panel meeting

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<sup>23</sup> Available at <https://pcori.fluxx.io/>.



and ensure that all applications receive a fair and thorough review informed by the standards outlined in the PFA.

### **In-Person Applicant Presentation**

Based on the results of merit review and PCORI's programmatic priorities, a selective subset of applicants whose proposed studies are deemed to be highly meritorious and/or aligned with PCORI's strategic priorities may be invited to the second phase of project presentation and follow-up discussions with PCORI on study methodological and execution issues. Applicants are also expected to address concerns and critiques identified in the merit review in this presentation. The selected applicants will be notified of the logistics, including travel arrangements for this presentation, in separate communications.

### **Post-Panel Review**

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

### **Summary Statements and Funding Recommendations**

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

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

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