Cycle 2 2020 Funding Cycle

PCORI Funding Announcements: Observational Analyses of Second-Line Pharmacological Agents in Type 2 Diabetes

Published May 5, 2020

This PCORI Funding Announcement (PFA) applies to the funding cycle that closes September 1, 2020, at 5 pm (ET). Submission Instructions, templates, and other resources are available at https://www.pcori.org/funding-opportunities/announcement/observational-analyses-second-line-pharmacological-agents-type-2-diabetes-cycle-2-2020.
About PCORI

The Patient-Centered Outcomes Research Institute (PCORI) was authorized by Congress in 2010 as a nonprofit, nongovernmental organization. PCORI’s purpose, as defined by our authorizing legislation, is to help patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders make better-informed health decisions by advancing the quality and relevance of evidence about how to prevent, diagnose, treat, monitor, and manage diseases, disorders, and other health conditions and by promoting the dissemination and uptake of this evidence.

PCORI is committed to transparency and a rigorous stakeholder-driven process that emphasizes patient engagement. PCORI uses a variety of forums and public comment periods to obtain public input to enhance its work. PCORI helps people make informed healthcare decisions and improves healthcare delivery and outcomes by producing and promoting high-integrity, evidence-based information that comes from research guided by patients and other stakeholders.

Patient-Centered Outcomes Research Institute
1828 L St., NW, Suite 900
Washington, DC 20036
Phone: 202-827-7700
Fax: 202-355-9558
Email: info@pcori.org

Follow us on Twitter: @PCORI
## Overview

<table>
<thead>
<tr>
<th>Published</th>
<th>May 5, 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key Dates</strong></td>
<td></td>
</tr>
<tr>
<td>Online System Opens:</td>
<td>May 5, 2020</td>
</tr>
<tr>
<td>Town Hall:</td>
<td>May 20, 2020, 12 pm (ET)</td>
</tr>
<tr>
<td>LOI Deadline:</td>
<td>June 2, 2020, by 5 pm (ET)</td>
</tr>
<tr>
<td>LOI Status Notification:</td>
<td>June 30, 2020</td>
</tr>
<tr>
<td>Application Deadline:</td>
<td>September 1, 2020, by 5 pm (ET)</td>
</tr>
<tr>
<td>Merit Review:</td>
<td>November 2020</td>
</tr>
<tr>
<td>Awards Announced:</td>
<td>March 2021</td>
</tr>
<tr>
<td>Earliest Project Start Date:</td>
<td>July 2021*</td>
</tr>
<tr>
<td><strong>Maximum Project Budget (Direct Costs)</strong></td>
<td>$4 million</td>
</tr>
</tbody>
</table>

At the time of contract execution, PCORI sets aside all of the funds associated with an awarded project to be made available throughout the contract’s period of performance. The maximum budget includes all research- and peer review–related costs. PCORI will not review submissions exceeding the stated maximum budget.

| Maximum Research Project Period | 3 years (36 months) |
| **Total Available Funds** | $20 million |

| **Eligibility** |  |
| Applications may be submitted by any private-sector research organization, including any nonprofit or for-profit organization, and 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. The Internal Revenue Service must recognize all US applicant organizations. Nondomestic components of organizations based in the United States and foreign organizations may apply, as long as there is demonstrable benefit to the US healthcare system, and US efforts in the area of patient-centered research can be shown clearly. Organizations may submit multiple applications for funding. Individuals are not permitted to apply. |

| **Review Criteria** |  |
| 1. Potential for the study to fill critical gaps in evidence |  |
| 2. Potential for the study findings to be adopted into clinical practice and improve delivery of care |  |
| 3. Scientific merit (research design, analysis, and outcomes) |  |
| 4. Investigator(s) and environment |  |
| 5. Patient-centeredness |  |
| 6. Patient and stakeholder engagement |  |

| **Contact Us** |  |
| **Programmatic Inquires:** Email (sciencequestions@pcori.org), phone (202-627-1884), or online (http://www.pcori.org/PFA/inquiry) |  |
| **Administrative, Financial, or Technical Inquiries:** Email (pfa@pcori.org) or phone (202-627-1885) |  |

PCORI will respond within two business days. However, we cannot guarantee that all questions will be addressed two business days prior to a Letter of Intent (LOI) or application deadline. Applicants are asked to plan accordingly; it is the applicant’s responsibility to submit the application on or before the application deadline.

*Update on July 2, 2020. The incorrect date (February 2021) was previously noted.*
# Table of Contents

I. Introduction ..................................................................................................................... 1
   - Summary of Program ........................................................................................................ 1
   - General Considerations for PCORI-Funded Research ....................................................... 2
   - Background .......................................................................................................................... 2
   - Funds Available and Duration of Studies ............................................................................ 5

II. Guidance for Preparing Responsive Applications ....................................................... 5
   - Specific Requirements for this Funding Announcement ..................................................... 5
   - Categories of Non-Responsiveness .................................................................................... 6
   - Studies of Cost Effectiveness ............................................................................................ 7
   - Coverage of Intervention Costs ......................................................................................... 7
   - Avoiding Redundancy ........................................................................................................ 7
   - Methodological Considerations ........................................................................................ 7
   - Leveraging Existing Resources, Including PCORnet ....................................................... 7
   - Patient and Stakeholder Engagement ............................................................................... 8
   - Populations Studied and Recruited .................................................................................. 9
   - Protection of Human Subjects .......................................................................................... 10
   - Required Education of Key Personnel on the Protection of Human Subject Participants .... 10

III. LOI Review .................................................................................................................. 10

IV. Merit Review ................................................................................................................ 11
   - Preliminary Review ............................................................................................................. 11
   - In-Person Review ............................................................................................................... 15
   - Post-Panel Review ................................................................................................................. 15
   - Summary Statements and Funding Recommendations ...................................................... 16

V. PCORI Policies that Govern Awardees Related to Data Access, Privacy, and Public Reporting ........................................................................................................... 16
   - Registering Research Projects .......................................................................................... 16
   - PCORI Public Access Policy .............................................................................................. 16
   - Standards for Privacy of Individually Identifiable Health Information ............................... 16
   - Data Management and Data-Sharing Plan ......................................................................... 17
   - Peer Review and Release of Research Findings ................................................................. 17
I. Introduction

Summary of Program

This initiative seeks to fund high-quality studies using observational designs that compare the effectiveness of newer and older second-line pharmacological agents used in metabolic control of individuals with type 2 diabetes mellitus (T2DM) at moderate cardiovascular risk (2-3 percent risk of events per year).

This funding initiative seeks to extend the evidence beyond existing results from randomized controlled trials published over the past five years. Findings from the EMPA-REG OUTCOME trial (empagliflozin; sodium glucose cotransporter 2 [SGLT2] inhibitor) in 2015 indicate that empagliflozin may have a cardiovascular protective effect in patients with T2DM at high risk for cardiovascular events.1 Subsequently, the LEADER (liraglutide; glucagon-like peptide-1 [GLP-1] receptor agonist),2 SUSTAIN-6 (semaglutide; GLP-1 receptor agonist),3 CANVAS (canagliflozin; SGLT2 inhibitor),4 and REWIND (dulaglutide; GLP-1 receptor agonist)5 trials all found an apparent cardiovascular benefit of either an SGLT2 inhibitor or a GLP-1 receptor agonist relative to placebo. These results have led to challenges for clinicians in choosing among an expanded range of medication choices for T2DM patients who no longer have acceptable metabolic control with metformin monotherapy. The available agents vary in costs to patients as well as their risks and side effect profiles.

PCORI is seeking applications for studies that compare multiple agents within newer medication classes (SGLT2 inhibitors and GLP-1 receptor agonists) and older, lower-cost medication classes (sulfonylureas, dipeptidyl peptidase 4 [DPP-4] inhibitors). The new studies should address whether individual agents or the entire class of second-line agents offer meaningful benefits in reducing cardiovascular disease outcomes in people with diabetes. These studies should determine with maximal precision the magnitude of any cardiovascular benefits and compare those benefits in patients whose baseline cardiovascular risk is lower than among those examined in the published clinical trials.

While additional large-scale randomized controlled trials on this topic would be desirable, such trials would require many years and substantial resources. Well-designed, methodologically robust observational studies that emulate a randomized trial, while not a substitute for clinical trials, have the potential to provide real-world evidence to inform clinical decision making over the short term. In addition, observational studies in this space may help inform the design of future trials and offer insights into the heterogeneity of treatment effects for different patient subgroups.

The new research supported by this program is intended to focus on the comparative risks and benefits

---

of the classes of drugs (and individual drugs within those classes), with a primary focus on cardiovascular outcomes. The envisioned primary outcomes of the study include 3-point major adverse cardiovascular events (MACE): non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the potential of a fourth point to include revascularization or hospitalization for heart failure. Other outcomes of interest include the individual components of MACE, all-cause mortality, glycemic control, renal function, medication side effects, weight gain or loss, and additional patient-centered outcomes (e.g., hypoglycemia). The potential observational study may also examine the incidence of microvascular complications (including new onset of diabetic retinopathy or early renal disease), the time to the introduction of second- and third-line agents, and the clinical events that precede drug switching.

General Considerations for PCORI-Funded Research

The Patient-Centered Outcomes Research Institute (PCORI) funds patient-centered outcomes research (PCOR), a type of comparative clinical effectiveness research (CER) that focuses on outcomes that matter to patients, their caregivers, and their families. PCORI-funded studies must include the perspectives of patients and other healthcare stakeholders.

PCORI is seeking applications designed to provide information that can inform critical decisions facing patients and caregivers, clinicians, policy makers, and healthcare system leaders. These decisions must be consequential and occurring now, in the absence of sound evidence about the comparative effectiveness of alternative approaches. Substantial potential must exist for patients and caregivers to benefit from the new knowledge in ways that are important to them. The premise of the research should be that the new knowledge will inform critical choices of patients and stakeholders in health care. This knowledge should offer insight about the comparative benefits and harms of the options and should provide information on outcomes that are important to patients.

The public entrusts PCORI to fund research that matters to patients, their caregivers, and other stakeholders (defined as clinicians and clinician societies, hospitals and health systems, payers [insurance], purchasers [business], industry, researchers, policy makers, and training institutions). By emphasizing the role of diverse research teams that include varying perspectives, PCORI seeks to change the way research is conducted. PCORI distinguishes itself by supporting research in which patients, caregivers, practicing clinicians, and the broader stakeholder community are actively engaged in generating research questions, reviewing research applications, conducting research, disseminating research findings, promoting the implementation of research findings, and using the results to understand and address patient and other stakeholder needs.

Background

The treatment of T2DM typically begins with lifestyle modification and the use of metformin, when indicated. When lifestyle modification and metformin are insufficient to control blood glucose levels, additional medications may be prescribed. Numerous classes of drugs are available for treating type 2 diabetes. These classes include sulfonylureas, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, and insulin. Individual drugs and medication classes vary in their benefits and potential harms and may also vary in their risks for individual patients.

Metformin is the consensus first-line pharmacologic treatment for type 2 diabetes, but clinical
guidelines provide less clarity regarding the choice of second-line therapies, especially for those individuals without established cardiovascular or kidney disease.\textsuperscript{6,7} While many randomized trials have been or are being conducted to establish the efficacy and effectiveness of the various second-line treatments for diabetes, important questions remain about their comparative effectiveness and safety. A particularly important concern is the effect of second-line agents on the risk of cardiovascular complications.

Emerging evidence from cardiovascular outcomes trials suggests that certain agents in newer drug classes may have a cardioprotective effect, in terms of ischemic heart disease, congestive heart failure, or both. These trials were mostly placebo-controlled studies rather than head-to-head comparisons of individual drugs or drug classes (see Table 1 for a list of trials). In addition, the trials generally enrolled patients with established cardiovascular disease or those at very high risk. The published trials do not clarify whether the cardiovascular benefit will be seen when newer agents are directly compared with other drug classes or when comparisons are conducted in populations with lower baseline cardiovascular risk.\textsuperscript{8} In the absence of such data, clinicians do not have firm evidence to guide the choice of second-line therapy for the many people with diabetes who do not have established cardiovascular disease. The intent of this PCORI funding program is to support research that provides new evidence that can potentially help fill these gaps in the evidence base.

Given the strong indications of SGLT2 inhibitors’ benefit on congestive heart failure outcomes, additional trials of these agents are being conducted among diverse patients with heart failure. These trials are included in Table 1 with an asterisk indicating they address a broad patient population with heart failure, including individuals with heart failure who do not have type 2 diabetes.

Although the cardiovascular outcomes trials were designed to examine cardiovascular safety, trials within the SGLT2 inhibitor class and an exploratory analysis of data from one of the GLP-1 receptor agonist trials indicated a positive renal benefit. This PCORI funding program will support research that addresses gaps in the evidence base regarding cardiovascular benefits, and, if possible, renal benefits.

Table 1: Cardiovascular Outcomes Trials: Second-Line Agents for T2DM: DPP-4 Inhibitors, GLP-1 Receptor Agonists, and SGLT2 Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DPP-4 Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alogliptin</td>
<td>EXAMINE\textsuperscript{9}</td>
<td>June 2013</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>SAVOR-TIMI 53\textsuperscript{10}</td>
<td>May 2013</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>GLP-1 Receptor Agonists</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sitagliptin</strong></td>
<td>TECOS(^{11})</td>
<td>March 2015</td>
</tr>
<tr>
<td><strong>Linagliptin</strong></td>
<td>CARMELINA(^{12})</td>
<td>January 2018</td>
</tr>
<tr>
<td><strong>Linagliptin</strong></td>
<td>CAROLINA(^{13})</td>
<td>August 2018</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>GLP-1 Receptor Agonists</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liraglutide</strong></td>
<td>LEADER(^{14})</td>
<td>December 2015</td>
</tr>
<tr>
<td><strong>Lixisenatide</strong></td>
<td>ELIXA(^{15})</td>
<td>February 2015</td>
</tr>
<tr>
<td><strong>Semaglutide</strong></td>
<td>SUSTAIN-6(^{16})</td>
<td>March 2016</td>
</tr>
<tr>
<td><strong>Exenatide</strong></td>
<td>EXSCEL(^{17})</td>
<td>April 2017</td>
</tr>
<tr>
<td><strong>Albiglutide</strong></td>
<td>HARMONY(^{18})</td>
<td>March 2018</td>
</tr>
<tr>
<td><strong>Dulaglutide</strong></td>
<td>REWIND(^{19})</td>
<td>August 2018</td>
</tr>
<tr>
<td><strong>Oral Semaglutide</strong></td>
<td>PIONEER-6(^{20})</td>
<td>September 2018</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SGLT2 Inhibitors</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Empagliflozin</strong></td>
<td>EMPA-REG(^{21})</td>
<td>April 2015</td>
</tr>
<tr>
<td><strong>Canagliflozin</strong></td>
<td>CANVAS(^{22})</td>
<td>February 2017</td>
</tr>
<tr>
<td><strong>Dapagliflozin</strong></td>
<td>DECLARE(^{23})</td>
<td>September 2018</td>
</tr>
<tr>
<td><strong>Ertugliflozin</strong></td>
<td>VERTIS CV(^{24})</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

**Additional Trials in Heart Failure**

| **Dapagliflozin** | DAPA-HF\(^{25}\) | July 2019 |

---


Empagliflozin | EMPEROR-Reduced\textsuperscript{26} | Ongoing
Empagliflozin | EMPEROR-Preserved\textsuperscript{27} | Ongoing

*These trials include individuals with heart failure, some of whom do not have a diagnosis of type 2 diabetes mellitus.

**Funds Available and Duration of Studies**

PCORI has allotted up to $20 million under this PFA to fund high-quality observational studies that are responsive to the key research question of interest. The proposed budget for studies under this initiative may be up to $4 million in direct costs, as appropriate. The maximum project period is three years (36 months).

II. **Guidance for Preparing Responsive Applications**

This section includes information intended to be useful for preparing applications. This guidance explains PCORI’s requirements for scientific and programmatic responsiveness under this funding announcement. For information related to administrative and technical requirements for Letter of Intent and application submission, please consult the PCORI Submission Instructions.

**Specific Requirements for this Funding Announcement**

All applications must address the following priority research question:

What is the comparative effectiveness of older and newer second-line therapies in a population of people with type 2 diabetes mellitus who have moderate cardiovascular risk (2-3 percent risk of events per year)?

Responsive applications must do the following:

- Compare four second-line classes of therapy for effects on cardiovascular events (SGLT2 inhibitors, GLP-1 receptor agonists, sulfonylureas, and DPP-4 inhibitors), ideally including comparisons of individual agents within one or more classes. Applicants should clearly specify the comparisons to be included. If it is not possible to compare all four classes, a strong justification is required.

- Propose robust methods for the study design, to emulate (to the greatest possible extent) a randomized controlled trial. For example, see this paper.

- Approaches other than trial emulation may be proposed and considered responsive if a clear rationale is provided articulating how the proposed approach appropriately controls for confounding.

- Consider the following guidance when proposing methods:
  - Describe the approaches to be used to account for potential confounding from non-compliance, discontinuation of the intervention, treatment switching, and other


PCORI Cycle 2 2020: Observational Analyses of Second-Line Pharmacological Agents in Type 2 Diabetes
longitudinal use scenarios. The validity of these approaches should be described.

- Clearly define approaches to handling missing data.
- Describe the approach used to validate measurements of treatment and potential confounders.
- Have a maximum study duration of 36 months. PCORI anticipates that sufficient retrospective observational data are available for investigators to address multiple comparisons of medication classes and individual medications in 36 or fewer months. A minimum of four years of follow-up data are required. In addition to the analysis of retrospective data, some prospective data collection is permitted to meet the four-year follow-up requirement if its collection can be completed within the 36-month study period of performance.
- Propose a study with a sufficiently large cohort and longitudinal follow-up to permit adequate statistical power for the proposed comparative analyses. In general, longer follow-up in a smaller, well-defined cohort is preferable to shorter follow-up in a larger cohort.

- Specify outcomes of interest with a primary focus on cardiovascular outcomes:
  - At a minimum, primary outcomes of the study should include 3-point MACE: non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the potential of revascularization or hospitalization for heart failure as additional endpoints.
  - Other outcomes of interest include the individual components of MACE, all-cause mortality, glycemic control, renal function, medication side effects, weight gain or loss, and additional patient-centered outcomes (e.g., hypoglycemia).

- Describe the data source(s) and/or linkages from which data will be obtained, detailing the capability to obtain the precise estimates of absolute risk from the proposed data set. The included description should include estimates of the completeness of the available data, including data on treatments and their determinants as well as the availability of baseline and time-varying covariates. An acknowledgement of any data elements for which missingness is likely to be a problem should also be included.

- Describe the extent and consistency of available data on patient characteristics to permit control of potential known confounders.

- Demonstrate endorsement and participation in the project by patients and other stakeholders.

Categories of Non-Responsiveness

PCORI discourages proposals in the following categories and will deem them non-responsive:

- Instrument development, such as new surveys, scales, and so on
- Pilot studies intended to inform larger efforts
- Studies that compare patient characteristics rather than clinical strategy options
Consistent with its authorizing law, PCORI does not fund research whose findings will include the following:

- Coverage, payment, or policy recommendations
- Payment or policy recommendations
- Creation of clinical practice guidelines or clinical pathways
- Establishment of efficacy for a new clinical strategy

Studies of Cost Effectiveness

PCORI will consider an application non-responsive if the proposed research does the following:

- Conducts a formal cost-effectiveness analysis of alternative approaches to providing care
- Directly compares the costs of care between two or more alternative approaches to providing care

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 care costs. For further information, please reference our cost-effectiveness analysis FAQs.

Coverage of Intervention Costs

In general, PCORI will not cover costs for study interventions that constitute the procedures, treatments, interventions, or other standard clinical care (“patient care”) that are being proposed for comparison in the research project (“patient care costs”).

Avoiding Redundancy

PCORI encourages potential applicants to review funded research at pcori.org. We intend to balance our funded portfolio to achieve synergy and avoid redundancy where possible.

Methodological Considerations

The PCORI Methodology Standards represent minimal requirements for the design, conduct, analysis, and reporting of scientifically valid, patient-centered outcomes research. Regardless of study design, applications must adhere to all relevant PCORI Methodology Standards, and all deviations need to be justified. Applicants should address additional best practice for the proposed research approach in the application for PCORI funding.

Leveraging Existing Resources, Including PCORnet

PCORI is interested in new research that derives data from a wide variety of sources and that uses study designs appropriate for the goals of the proposed project. PCORI encourages investigators to propose studies that leverage existing resources, such as adding PCOR to an existing large clinical trial or analyzing existing large databases that contain valuable, relevant information that may be used to answer important CER questions. Another possible resource is established patient outcomes registries, especially when such registries can be linked to electronic medical record data from healthcare delivery systems.

28 Available at http://www.pcori.org/sites/default/files/PCORI_Authorizing_Legislation.pdf/.
systems or administrative claims data from public or commercial insurers. In circumstances in which randomized control trials are not practical or ethically acceptable, studies leveraging established patient outcomes registries can have meaningful and complementary roles in evaluating patient outcomes. PCORI does not intend for this PFA to support the development of new data networks or patient registries, but rather to support the effective utilization of existing data resources for proposed new CER studies.

For some proposed projects, the data resources of PCORnet, the National Patient-Centered Clinical Research Network, may be particularly appropriate. Over the past six years, PCORI has made a major commitment to create the infrastructure of PCORnet, which was designed to improve the nation’s capacity to conduct efficient large-scale clinical research and to learn from the healthcare experiences of millions of Americans. This large clinical research network represents patients, clinicians, health systems, and health plans across the country and supports research that will improve health care and health outcomes. The network currently includes nine clinical research networks, representing more than 100 health systems, two health plan research networks, a coordinating center, and a central office. PCORnet provides access to large longitudinal data sets that enhance the capture of relevant outcomes and provide more detail on specific procedures or treatments, disease severity, and the presence of comorbid illness.

The following elements are central to the rationale for and the sustainability of PCORnet:

- Preexisting, standardized, curated, and research-ready clinical data on large numbers of patients with specific clinical conditions and illnesses
- Actively engaged patients who join in governing the research uses of these data
- Distributed (rather than centralized) data platforms that maximize the security and local control of all data
- A readiness among network members to collaborate and a willingness to share data in pursuit of worthy research aims
- The capacity to link data across sources at the individual patient level

Applicants are encouraged to consider whether using PCORnet might assist in one or more aspects of their proposed research study. Examples include, but are not limited to, the following:

- Background to the research question or feasibility of the study
- Documenting the importance of the research question
- Estimating the size of the potentially eligible population
- Determining the range of current treatment practices and sequencing
- Assessing the duration of continuous treatment and care

**Patient and Stakeholder Engagement**

In PCORI-funded research, patients and other healthcare stakeholders are viewed as partners who leverage their lived experience and/or professional expertise to influence research to be more patient-centered.
centered, relevant, and useful. Engagement approaches and practices vary from project to project based on the patient population, the setting, and the needs of a study. PCORI encourages study teams to be creative in their methods for engaging with research partners. Effective involvement of patients and other stakeholders requires a well thought out engagement plan that includes the goals for engagement and information on who will be involved, what preparation will be provided, points and intensity of involvement, and the decision-making process.

**Populations Studied and Recruited**

PCORI seeks to fund research that includes diverse populations regarding age, gender, race, ethnicity, geography, or clinical status, so that possible differences in outcomes may be examined in defined subpopulations. PCORI recognizes that some proposed studies might represent important PCOR opportunities, even in the absence of a broadly diverse study population. However, the burden is on the applicant to justify the study’s importance in the absence of diversity; to discuss which subgroups are most important; and to discuss how the subgroups will be analyzed, including whether the study will be powered to examine the question of effectiveness in subgroups.

PCORI is particularly interested in including previously understudied populations for whom effectiveness information is especially needed, such as hard-to-reach populations or patients with multiple conditions. Thus, comparisons should examine the impact of the strategies in various subpopulations, with attention to the possibility that the strategy’s effects might differ across subpopulations. PCORI has developed the following list of populations of interest to guide our efforts in research and engagement:

- Racial and ethnic minority groups
- Low-income groups
- Women
- Children (0–17 years of age)
- Older adults (65 years of age 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, or limited English proficiency
- Gender and sexual minorities
- Veterans and members of the Armed Forces and their families

Regardless of the population studied, investigators are expected to provide evidence-based estimates regarding the representativeness of the potential pool of participants on which the study will be based, the target sample size, and data availability in light of the study’s inclusion and exclusion criteria as well...
as factors that may impact the final sample size (e.g., loss to follow-up).

**Protection of Human Subjects**

PCORI follows the Federal Policy for the Protection of Human Subjects (45 CFR part 46), including the Common Rule. For more detailed information, please see Section 5, “Human Subjects Research Policy,” in the **Supplemental Grant Application Instructions for All Competing Applications and Progress Reports**, which is issued by the US Department of Health and Human Services (HHS). In referencing the HHS Supplemental Grant Application Instructions, note that PCORI does not require that applicants comply with sections of the policy that refer to requirements for federal-wide assurance and the inclusion of women, minorities, and children in the proposed studies. Instead, PCORI expects applicants to address diversity in study participants in the research plan, through a focus on subpopulations, as described in the above section on **Populations Studied and Recruited**. Awardees must also comply with appropriate state, local, and institutional regulations and guidelines pertaining to the use of human subjects in research.

PCORI requires awardees to ensure that there is a Data and Safety Monitoring Plan, which may include the need to appoint a Data and Safety Monitoring Board, as provided in the **PCORI Policy on Data and Safety Monitoring Plans for PCORI-Funded 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**). Reviewers’ comments on human subject research are not reflected in the overall application score, but PCORI staff might use them during potential funding negotiations. Final determinations about the adequacy of human subject protections rest with the Institutional Review Board or international equivalent that has jurisdiction over the study.

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

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

PCORI requires that all applicants adhere to the National Institutes of Health (NIH) policy on education in the protection of human subject participants in the conduct of research. This applies to all individuals listed as key personnel in the application. The policy and FAQs are available on the **NIH website**.

### III. LOI Review

Applying for funding from PCORI is a two-stage process. An LOI must be submitted and an applicant must be invited to submit an application.

LOIs are evaluated based on the following:

- Importance and relevance of the topics to PCORI priorities, as evidenced by critical gaps

---

29 See [http://grants.nih.gov/sites/default/files-supplementalinstructions.docx](http://grants.nih.gov/sites/default/files-supplementalinstructions.docx)
identified by clinical guidelines developers and recent systematic reviews

- Clarity and credibility of responses to the LOI questions
- The investigators’ prior relevant experience
- Programmatic fit and balance, considering whether the LOI overlaps with previously funded studies or concurrent LOIs and/or applications to a significant degree or, conversely, whether the application fills a gap in the portfolio with certain characteristics, including disease category, topics, priority population, methodologies, and other variables

Only applicants whose LOIs are deemed most responsive to this PFA will be invited to submit a full application. A minimum of two PCORI staff review the LOIs, which are not scored during review.

The LOI Template provides guidance on responding to each item. Please refer to the Submission Instructions for information on how to submit an LOI via PCORI Online.

IV. Merit Review

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

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

PCORI merit review is a multiphase process that includes the review panel’s preliminary review of full applications and an in-person panel discussion of a subset of applications (identified by PCORI’s Program staff and based on the preliminary review and program priorities). After merit review, key steps include post-panel review of application by PCORI staff; the Selection Committee’s recommendation of applications for funding; and, finally, Board award approval.

Preliminary Review

PCORI conducts rigorous merit review of the full applications it receives. Note that PCORI may eliminate applications from the review process for administrative or scientific reasons (e.g., non-responsiveness). An application may be administratively withdrawn if it is incomplete; submitted past the stated due date and time; or does not meet the formatting criteria outlined in the Submission Instructions, in the PCORI templates, and in PCORI Online. An application may be scientifically withdrawn if it is not responsive to the guidelines described in this PFA, describes research that is not comparative, includes a cost-effectiveness analysis, or otherwise does not meet PCORI programmatic requirements.
PCORI Merit Review Officers (MROs) recruit each review panel based on the number of invited LOIs and topic areas represented by the invited LOIs. MROs recruit the panel chair, scientist reviewers who are subject matter experts, patient representatives, and representatives of other stakeholder groups. All panel members receive training during the review cycle to ensure that they understand the programmatic and organizational goals of review.

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

<table>
<thead>
<tr>
<th>Crosswalk of PCORI Merit Review Criteria with NIH Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIGNIFICANCE</td>
</tr>
<tr>
<td>1. Potential for the study to fill critical gaps in evidence</td>
</tr>
<tr>
<td>2. Potential for the study findings to be adopted into clinical practice and improve delivery of care</td>
</tr>
<tr>
<td>APPROACH</td>
</tr>
<tr>
<td>3. Scientific merit (research design, analysis, and outcomes)</td>
</tr>
<tr>
<td>4. Investigator(s) and environment</td>
</tr>
<tr>
<td><strong>PCORI-Only Merit Review Criteria</strong></td>
</tr>
<tr>
<td>PATIENT-CENTEREDNESS/ENGAGEMENT</td>
</tr>
<tr>
<td>5. Patient-centeredness</td>
</tr>
<tr>
<td>6. Patient and stakeholder engagement</td>
</tr>
</tbody>
</table>

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

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

The application should address the following questions:

- Does the application appropriately address the priority research question posed in this funding announcement?
- Will the application contribute toward filling a critical gap in current knowledge?

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

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

- Does the application identify who will make the decision (i.e., the decision maker) or use (i.e., the end-user) the findings (not the intervention) that this study produces, such as local and national stakeholders?
• Does the application identify potential end-users of study findings—such as local and national stakeholders—and describe strategies to engage these end-users?
• Does the application provide information that supports a demand for this kind of a study from end-users?
• Would this study’s research findings have the potential to inform decision making for key stakeholders? If so, provide an example. How likely is it that positive findings could be reproduced by others, resulting in improvements in practice and patient outcomes? Identify the potential barriers that could hinder adoption of the intervention by others.
• Does the application describe a plan for how study findings will be disseminated beyond publication in peer-reviewed journals and at national conferences?

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

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

• Does the application describe a robust observational study that emulates a randomized trial responsive to the priority comparative research question outlined in this funding announcement?
• Is each proposed comparison described clearly and well justified?
• Does the research plan describe rigorous methods that demonstrate adherence to the PCORI Methodology Standards?
• Is the proposed data set sufficiently complete to conduct the proposed analyses? Are data on potential confounders available, including repeated measures for data that can vary over time?
• Does the application provide justification that the outcome measures are validated and appropriate for the population?
• Are the sample sizes and power estimates appropriate and well justified? Do the proposed data sources include sufficient duration of follow-up to conduct the proposed analyses?
• Is the study plan feasible? Is the project timeline realistic, including specific scientific and engagement milestones?

**Criterion 4. Investigator(s) and environment**

This criterion assesses the appropriateness (e.g., qualifications and experience) of the investigator(s)/team and the environment’s capacity (e.g., resources, facilities, equipment) to support the proposed project.

The application should also address the following questions:

• How well qualified are the Principal Investigators (PIs), collaborators, and other researchers to conduct the proposed activities?
Does the research team include individuals with the skillsets necessary to emulate a randomized trial using observational data? Are appropriate partnerships with individuals who have relevant methodologic expertise in place?

Does the research team have experience linking data sources to conduct an analysis of the proposed scale and scope?

If the project is collaborative or dual-PI, do the investigators have complementary and integrated expertise? Are the leadership, governance, and organizational structures appropriate for the project?
  o (Dual-PI Option Only) Does the Leadership Plan adequately describe and justify PI roles and areas of responsibility?

Is the level of effort for each team member appropriate for successfully conducting the proposed work?

Is the institutional support appropriate for the proposed research?

**Criterion 5. Patient-centeredness**

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

The application should also address the following questions:

- Does the application include a thorough description about which outcomes (both benefits and harms) are important to patients, and are those outcomes included in the study plan?

- Are the proposed comparisons (including comparisons of specific agents within a drug class) of interest to patients, clinicians, and other stakeholders?

**Criterion 6. Patient and stakeholder engagement**

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

The application should also address the following questions:

- Does the application provide a well-justified description of how the research team incorporates stakeholder involvement? Does the study include the right individuals (e.g., patients, caregivers, clinicians, policy makers, hospital and health system representatives, payers, purchasers, industry, researchers, training institutions) to ensure that the projects will be carried out successfully? Is there justification for why these stakeholders were selected? Do stakeholders represent the groups of people most impacted by the problem the study addresses, including
the most vulnerable?

- Does the application show evidence of active engagement among scientists, patients, and other stakeholders throughout the research process (e.g., formulating questions, identifying outcomes, monitoring the study, disseminating and implementing the study findings)? Are the frequency and level of patient and stakeholder involvement sufficient to support the study goals?

- Is the proposed engagement approach appropriate and tailored to the study and target population?

- Are the roles and the decision-making authority of all study partners described clearly?

- Are the organizational structure and resources appropriate to engage patients and stakeholders throughout the project?

In-Person Review

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

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

Post-Panel Review

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

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

Summary statements are provided to applicants approximately two weeks before funding decisions are announced. If an application progresses to in-person discussion, the applicant will receive a summary statement, which will include the following:

- In-person panel discussion notes
- Final average overall score
- Preliminary reviewer critiques
- Application quartile, to help applicants understand how their application scored to other discussed applications, as appropriate

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

Funding recommendations are made by identifying meritorious applications that fit the programmatic needs and that satisfactorily address the merit review criteria while adhering to the PCORI Methodology Standards. Programs also consider the funds allotted for the current funding announcement when deciding which applications to recommend to the Board for approval. Applicants to this current cycle’s PFA will receive summary statements and notification of the funding status of their application no later than March 2021.

V. PCORI Policies that Govern Awardees Related to Data Access, Privacy, and Public Reporting

Applicants should be aware that all PCORI awardees are required to comply with the following requirements:

Registering Research Projects

PIs are required to use the naming convention “PCORI-PCORI application number” (i.e., PCORI-XXXX-XXXXX). Clinical trials must be registered before enrollment of the first patient. All trials that meet the definition on the NIH database33 (see Data Element Definitions) are required to register, if funded.

Funded clinical trials or observational outcomes studies must be registered at ClinicalTrials.gov.

Any patient registries used in this study must be registered at https://patientregistry.ahrq.gov/.

PCORI Public Access Policy

PCORI requires all awardees to adhere strictly to PCORI’s publication policies, which will be shared with awardees within the research contract.

Standards for Privacy of Individually Identifiable Health Information

On August 14, 2002, the Department of Health and Human Services issued a final modification to the Standards for Privacy of Individually Identifiable Health Information, the “Privacy Rule.” The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

33 Available at https://prsinfo.clinicaltrials.gov/.

PCORI Cycle 2 2020: Observational Analyses of Second-Line Pharmacological Agents in Type 2 Diabetes
that governs the protection of individually identifiable health information and is administered and enforced by the HHS Office for Civil Rights.

Decisions about the applicability and implementation of the Privacy Rule reside with the researcher and his or her institution. The Office for Civil Rights provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools related to “Am I a covered entity?” Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding and progress monitoring of grants, cooperative agreements, and research contracts is available from NIH.

Data Management and Data-Sharing Plan

PCORI is committed to publishing and disseminating all information and materials developed using PCORI funding, in accordance with its authorizing legislation. All recipients of PCORI contracts must agree to these principles and take steps to facilitate data availability.

PCORI encourages openness in research and making research data available for purposes of replication and reproducibility. As such, if an award is made, the awardee will be expected to adhere to PCORI’s Policy for Data Management and Data Sharing. The policy articulates PCORI’s requirement that certain awardees make the underlying data and data documentation (e.g., study protocol, metadata, analytic code) from their PCORI-funded research projects available to third-party requestors.

A full data management and data sharing plan is not required at the time of application. If an award is made, the awardee is required to develop and maintain such a plan, which is described in detail in the PCORI Methodology Standards for Data Integrity and Rigorous Analyses, specifically Standard IR-7. This plan must be appropriate for the nature of the research project and the types of research project data, and consistent with applicable privacy, confidentiality, and other legal requirements. The policy includes details about what data certain awardees will be expected to deposit into a PCORI-designated repository and when that data would be available for third-party requests.

The information here is meant for informational purposes only and does not attempt to be an exhaustive representation of the Policy for Data Management and Data Sharing. Please refer to the policy in its entirety for additional information.

Peer Review and Release of Research Findings

PCORI has a legislative mandate to ensure the scientific integrity of the primary research it supports and to make study findings widely available and useful to patients, clinicians, and the general public within a specific timeframe. Accordingly, the PCORI Board of Governors adopted the Process for Peer Review of Primary Research and Public Release of Research Findings.

In summary, awardee institutions are required to submit to PCORI for peer review a draft final research report that provides the methodological details, describes the main study results, and interprets the findings in clinical or other decisional contexts. After awardee institutions have responded to reviewers’ comments to PCORI’s satisfaction, the report will be accepted and considered final. PCORI will then

34 Available at http://www.hhs.gov/ocr/.
prepare two 500-word standardized abstracts summarizing the study results (as detailed below), which the awardee institution will review and approve.

No later than 90 days after the draft final research report is accepted, PCORI will post the following materials on its website: (1) a 500-word abstract for medical professionals; (2) a 500-word standardized abstract summarizing the study results for patients and the general public; (3) a link to the study record on ClinicalTrials.gov (as applicable); and (4) ancillary information, including conflict of interest disclosures. The final research report, along with anonymized reviewer comments, will be made publicly available on the PCORI website no later than 12 months after its acceptance, except by prior mutual agreement with the awardee institution.