PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

Cycle 3 2024

Promoting Healthy Children and Youth

Topical PCORI Funding Announcement (PFA)

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This Topical PCORI Funding Announcement (PFA) applies to the funding cycle that closes January 14, 2025, at 5 pm ET. Submission Instructions, templates, and other resources are available at https://www.pcori.org/funding-opportunities/announcement/promoting-healthy-children-and-youth-topical-pcori-funding-announcement-cycle-3-2024.

About PCORI

The Patient-Centered Outcomes Research Institute (PCORI) is the nation's leading funder of patient-centered comparative clinical effectiveness research (CER). By comparing two or more health or health care approaches, CER generates evidence that helps people make better-informed decisions and improves health care delivery and outcomes. PCORI takes a holistic approach to its work, ensuring that patients and other health decision makers are engaged as partners throughout the research process, supporting dissemination and implementation of results in practice and strengthening clinical research infrastructure to advance patient-centered CER. PCORI is an independent, nonprofit organization authorized by Congress.

PCORI's funding announcements align with PCORI's National Priorities for Health as a means of ensuring applications address the health and health care challenges facing the nation today and in the years ahead. PCORI's National Priorities for Health are a comprehensive set of mutually reinforcing goals that focus on impact, and drive research funding and other initiatives to improve patient care and health outcomes. PCORI's Topic Themes speak to the everyday health issues facing large numbers of people in the United States, including children, youth and older adults, and address urgent topics such as substance use, mental and behavioral health and violence and trauma, as well as widespread conditions including cardiovascular disease, pain management and sleep health. These current themes include four ongoing topics — preventing maternal morbidity and mortality, improving outcomes for people with intellectual and developmental disabilities, addressing COVID-19 and addressing rare diseases. Intentionally broad and intersectional, the themes will be further refined over time to adapt to the evolving health and health care landscape.

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Key Dates	**Online System Opens:** Sept. 4, 2024 **Town Hall:** Sept. 18, 2024, at noon – 1 pm (ET) **Letter of Intent (LOI) Deadline:** Oct. 1, 2024, by 5 pm (ET) **LOI Status Notification:** Oct. 29, 2024 **Application Deadline:** Jan. 14, 2025, by 5 pm (ET) **Merit Review:** March 2025 **Awards Announced:** July 2025 **Earliest Project Start Date:** November 2025
Maximum Project Budget (Direct Costs)	Up to $12 million At the time of contract execution, PCORI sets aside all 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.**
Maximum Research Project Period	Up to five years* *PCORI expects that most proposals responding to this funding announcement will be less than or equal to five years in duration. In exceptional circumstances, PCORI will consider applications that propose projects up to seven years in duration, with strong justification, provided that they aim to assess longer-term outcomes and demonstrate that the proposed study duration is critical to answering the proposed CER question. Such applications must have a plan for the collection and analysis of longer-term data at least 24 months from baseline for at least one primary outcome for all participants as well as a compelling rationale for why the primary outcome(s) would benefit from and/or require that length of follow-up. **Requests to exceed the maximum project period will be reviewed with the submitted LOI. PCORI approval of an increased study duration is required at the LOI stage before application submission. Applications that exceed the 5-year maximum project period without prior PCORI approval will be administratively withdrawn and not forwarded for further review.**
Funds Available up to Approximately	$100 million
Eligibility	In general, applications for the conduct of research and management of funding may be submitted by appropriate academic research, private sector research, or study-conducting entities. This may include, among others, agencies and instrumentalities of the federal government, nonprofit and for-profit research organizations, and colleges and universities.

	Per PCORI's authorizing statute, every applicant must demonstrate capability to comply with the following conditions: abide by the transparency and conflicts of interest requirements that apply to PCORI with respect to the research managed or conducted under contract; comply with the PCORI methodological standards adopted by the Board of Governors; consult, as appropriate, with the expert advisory panels for clinical trials and rare disease; deposit de-identified data from the original research into a PCORI-designated repository to facilitate data sharing, as appropriate; have appropriate processes in place to manage data privacy and meet ethical standards for the research; comply with the requirements of PCORI for making the information available to the public; and comply with other terms and conditions determined necessary by PCORI to carry out the research project. Potential applicants are strongly encouraged to review the standard research contract prior to application. ***Individuals are not permitted to apply.*** Foreign organizations and nondomestic components of US organizations must provide a thorough and thoughtful justification for the research's ability to benefit the US healthcare system and that the engagement plans include US patients and stakeholders and are relevant to the US healthcare system.
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	**Scientific/Research Leads:** Andrea Brandau, MPP; Jennifer Cooper, PhD, MS **Programmatic Inquiries:** sciencequestions@pcori.org or the online office hours link. **Note:** In order to promptly address your inquiry, any questions received will be directed to the most suitable staff member within PCORI, regardless of whether they are the designated lead for this funding announcement. **Technical Inquiries:** Contact the PCORI Helpdesk at pfa@pcori.org for quickest assistance. The PCORI Helpdesk can also be reached at 202-627-1885. PCORI typically will respond to all inquiries within two business days. However, PCORI cannot guarantee a response to questions posed within the two business days prior to a Letter of Intent (LOI) or application deadline. Applicants must plan accordingly; it is the applicant's responsibility to submit by stated submission deadlines.

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I. Introduction

Summary

This Topical PFA seeks to fund patient-centered comparative clinical effectiveness research (CER) projects that focus on interventions that improve patient-centered outcomes in children and youth. PCORI is particularly interested in applications focusing on the following Special Areas of Emphasis (SAEs): prevention and treatment of obesity, addressing social determinants of health and social needs to improve health outcomes, and targeted prevention of substance misuse through identified risk factors. However, applications are not limited to these areas.

This PFA solicits applications focused on children and youth. Proposals should focus on children and youth residing in the United States who are 0 to 24 years old. Applications proposing interventions that involve parents and caregivers are acceptable. Studies that propose to evaluate interventions targeting parents or caregivers that do not include a primary outcome measure of child and youth health or well-being will be considered nonresponsive to the funding announcement. Applicants may propose comparative effectiveness studies of prevention, screening, diagnostic, treatment and management approaches, and pharmacologic, nonpharmacologic, and/or combination therapies, as appropriate. Studies may also focus on improving system-level strategies delivered in hospitals, clinics or community settings to improve patient-centered outcomes. Applicants are strongly encouraged to propose individual or cluster randomized controlled trials (RCTs); however, well-specified natural experiments and rigorous observational studies will also be considered. Proposed studies should examine diverse populations with an overall sample size sufficient to allow for precision in estimating hypothesized effect sizes and, as appropriate, analysis of heterogeneity of treatment effects. Applicants are strongly encouraged to assess issues of intervention implementation to facilitate widespread uptake of findings after completion of the study. Toward that end, hybrid type 1 and hybrid type 2 trials may be appropriate. Hybrid type 3 trials, as well as strict implementation or dissemination studies, will not be considered responsive, nor will studies focused on the development of research methods. Applicants should propose well-justified and validated outcomes that are clinically meaningful and considered important by patients and that can be affected by the proposed interventions within the study duration.

National Priorities for Health: Invited Areas for Investigator-Initiated Research

PCORI invites applications addressing patient-centered CER questions that meet the scope and intent of this PFA and align with at least one of four of PCORI's National Priorities for Health. The remaining National Priority, Enhance Infrastructure to Accelerate Patient-Centered Outcomes Research, is covered by other PCORI funding opportunities.

Applicants must address and self-designate their alignment with at least one of PCORI's National Priorities for Health but may also designate a secondary and tertiary National Priority for Health goal that aligns with their proposed research. Selecting more than one National Priority for Health confers no competitive advantage but serves to guide appropriate review for the proposed research.

To be considered responsive, applicants must propose research that meets this PFA'S distinctive requirements and addresses at least one of the following National Priorities for Health:

- Increase Evidence for Existing Interventions and Emerging Innovations in Health
  - Goal: Strengthen and expand ongoing CER focused on both existing interventions and emerging innovations to improve health care practice, health outcomes, and health equity.
- Accelerate Progress Toward an Integrated Learning Health System
  - Goal: Foster actionable, timely, place-based, and transformative improvements in patient-centered experiences, care provision, and improved health outcomes through collaborative, multisectoral research to support a health system that understands and serves the needs and preferences of individuals.
- Achieve Health Equity
  - Goal: Expand stakeholder engagement, research, and dissemination approaches that lead to continued progress toward achieving health equity in the United States.
- Advance the Science of Dissemination, Implementation, and Health Communication
  - Goal: Advance the scientific evidence for and the practice of dissemination, implementation, and health communication to accelerate the effective sharing of CER results for public understanding and uptake into practice.

Applicants will be asked to select one of these four National Priorities as primary, and if relevant, a secondary and/or tertiary National Priority in their Letter of Intent (LOI) and, if invited, full application.

PCORI has several Topic Themes of interest that inform PCORI's funding opportunities. The Topic Themes speak to everyday health issues facing large numbers of people in the United States including children, youth, and older adults and address urgent topics such as substance use, mental and behavioral health, violence and trauma, as well as widespread conditions including cardiovascular disease, pain management, and sleep health. These themes include four key topics that have been important interest areas for PCORI—preventing maternal morbidity and mortality, improving outcomes for people with intellectual and developmental disabilities (IDD), addressing COVID-19, and addressing rare disease.

In LOIs and applications, applicants must identify whether their proposed research aligns with any additional Topic Themes beyond the Promoting Healthy Children and Youth Topical. As applicable, applicants should designate secondary and tertiary Topic Themes with which their project most closely aligns (if any). If more than one Topic Theme applies, designate the primary as Promoting Healthy Children and Youth and any secondary and/or tertiary Topic Theme(s) as appropriate. The purpose of identifying these Topic Themes is to encourage submissions to these areas, not to limit submissions to only these themes. The Topic Themes, clustered into three groups, are as follows:

Populations

1. Improving outcomes for people with intellectual and developmental disabilities (IDD)
2. Promoting health for older adults
3. Promoting healthy children and youth

Health Behaviors

4. Addressing substance use
5. Addressing violence and trauma

Health Conditions

6. Addressing COVID-19
7. Addressing rare diseases
8. Improving cardiovascular health
9. Improving mental and behavioral health
10. Managing pain
11. Preventing maternal morbidity and mortality (MMM)
12. Promoting sleep health

Additional information about the Topic Themes and examples of projects are available on the PCORI website.

Topic Background and Evidence Gaps

PCORI uses the World Health Organization's definition of children and youth, defined as persons 0 to 24 years old.[1] In the United States today, children and youth comprise more than 30 percent of the population[2,3] and are the most racially and ethnically diverse age group, with less than half of children and youth being non-Hispanic white.[4] Individuals within this population face multiple challenges to their mental and physical health. Rates of mental illness have increased significantly in recent years for this population and have been exacerbated by the growing shortage of mental health professionals.[5] Pediatric obesity prevalence remains high at nearly 20 percent and disproportionally affects Black and Hispanic youth.[6] Nearly 2 million adolescents were estimated to have a drug use disorder in 2022, and there has been a dramatic rise in drug overdose deaths in adolescents in recent years.[7,8] Children and youth also constitute the poorest segment of the U.S. population.[9] This high poverty rate, and the social and structural inequities underlying it, are significant drivers of child morbidity and mortality. The rate of mortality in children and youth has increased since the start of the COVID-19 pandemic, driven by injuries (largely those resulting from violence and self-harm), and drug misuse.[10] The promotion of health for this large and diverse population requires interventions across the care continuum, including supporting optimal growth and development, screening and prevention, treatment of acute and chronic illnesses, and the transition to adult care. Compared to adults, available choices of interventions for children and youth may be distinctive and varied based on their stage of physical, cognitive, and emotional maturity. Multiple systems and external structures also influence child health, development, and functioning and can facilitate or impede successful health outcomes. Optimally addressing social determinants of health that can often pose barriers to health care access, quality, and equity is particularly important for this population.

PCORI has received significant input from diverse stakeholders, including patient and caregiver advocates, clinicians and health care providers, payers, researchers, and other research funders in the area of children's health. Overarching emphasis was placed on the need for real-world CER across the pediatric care continuum that informs evidence-based clinical practice as well as an enhanced understanding of how to best leverage community partnerships to improve care. The PCORI external community and the scientific literature have highlighted several evidence gaps and

identified targets for CER to promote the health of children and youth in the areas of pediatric obesity, social determinants of health, and substance misuse.

Prevention and treatment of obesity: Obesity is a complex disease associated with sequelae that can impair a child's well-being and quality of life during a critical time for growth and development. Children and adolescents with obesity have a higher prevalence of comorbidities and a greater risk for obesity during adulthood.[11] Existing literature on pediatric obesity has largely focused on treatment rather than prevention,[12] which signifies the need for more patient-centered CER focused on prevention, particularly targeting younger age groups, such as infants, toddlers and school-age children.[13] Family-based lifestyle change interventions that involve parents to promote behavior change have been shown to be efficacious at preventing and controlling childhood overweight and obesity.[14] However, several studies have reported poor intervention participation and engagement as a challenge and limitation to affect child weight outcomes.[15] There is a need to examine the potential impact of less burdensome low-intensity interventions, especially among socioeconomically disadvantaged families — as well as interventions designed to improve engagement in family-based childhood obesity interventions to increase effectiveness and durability of outcomes.[16,17,18] Multicomponent interventions that combine physical activity, nutrition and behavioral change components appear to be the most effective in preventing and reducing overweight and obesity in children.[19] However, more research is needed on how to optimize the combination and sequencing of multiple intervention components, recognizing that such optimization may vary across populations.[20] Regarding population-level interventions, there has been emerging evidence over recent decades on the impact of food and physical activity-related initiatives and strategies resulting from local, state or federal policies on childhood obesity. However, significant variation remains in policy and practice across states and localities, which offers an opportunity for CER to evaluate clinical and care delivery strategies associated with policy and practice variations using robust observational designs.[21,22] Many children and adolescents with obesity do not receive intensive health behavior and lifestyle treatment recommended by the U.S. Preventive Services Task Force and the American Academy of Pediatrics because of access barriers and scarcity of such treatment programs.[23] Further research is needed to improve access to guideline-concordant obesity interventions for children in underresourced communities. Several evidence gaps remain regarding the use of anti-obesity pharmacotherapy as an adjunct to intensive health behavior and lifestyle treatment.[24] Further research should explore the timing of initiation, duration of therapy, combinations of therapies and lifestyle supports associated with these therapies. The long-term use and health effects of pharmacotherapies, such as glucagon-like peptide 1 medications in children and adolescents with high body mass index (BMI), has also been identified as an area in need of further evaluation.[25,26] Few pediatric studies have investigated long-term weight maintenance after the initial, more intensive weight loss phase.[27] Future studies should include longer follow-up periods after the cessation of treatment[28] to assess long-term outcomes and long-lasting effects of interventions.

Addressing social determinants of health and social needs to improve health outcomes: Many studies focused on children and their caregivers have demonstrated the efficacy of interventions targeting social determinants of health (SDOH) and social needs.[29] Such studies have shown the positive effects on child health and health care use of, for example, clinic-based screening of families for social needs and the provision of referrals to community-based resources, legal services or patient navigation services to assist families in meeting their social needs.[30,31,32] Studies have also demonstrated the positive impacts on child health of partnerships between health systems and community organizations to improve housing, food and other resources in underserved

communities.[33,34] Despite this evidence, however, most studies have focused on process measures rather than health outcomes. In addition, many studies to date have focused on screening and referral processes, yet inadequate evidence remains on whether SDOH screening accurately assesses a child's social needs and which interventions after screening best address children's various social needs and produce lasting improvements in overall health.[35] In addition, many studies to date have been pre-post observational studies, and few have been CER studies. Future studies using rigorous RCT or observational designs will help address the evidence gap. Importantly, the health care system cannot by itself address the effects of children's social needs on their health. Partnering with community organizations and other stakeholders is essential to address the root causes of health inequities and achieve improvements in pediatric population health. There is a need for medical-community partnerships that streamline connectivity to services for underserved families.[36] There is also a need for more effective strategies incorporating anti-racist interventions to reduce racial and ethnic disparities in children's SDOH and social needs.[37]

Targeted prevention of substance misuse through identified risk factors: Adolescence is a critical period for physical and psychological development and is also a susceptible time for the initiation of substance misuse. Early onset of substance use is significantly associated with negative outcomes in adolescence and into adulthood, such as the development of a substance use disorder (SUD), psychosocial problems, and risky sexual behavior.[38] Thus, timely prevention (e.g., selective and indicated) interventions are imperative to avoid and address substance misuse as early as possible and to mitigate associated negative outcomes. There is a need for CER that evaluates evidence-based prevention strategies that can reduce substance misuse or mitigate substance use-related harms among youth with individual, interpersonal, and/or macrolevel risk factors for SUD. Opioids are frequently prescribed to children and adolescents to treat postinjury or surgery pain, which is the first exposure to opioids for many youths. However, a significant proportion of adolescents with access to prescribed opioids misuse or divert them (e.g., trade, sell, give away to others).[39] Prescription opioids are a known risk factor for the development of future illicit opioid use among adolescents, with high-dose and long-duration opioid prescriptions associated with increased overdose risk.[40,41,42] Although clinical guidelines for opioid prescribing exist for adults, they do not include recommendations specific to youth. However, guidelines for particular surgical procedures are available.[43,44,45] In addition to children and youth with pain after a traumatic injury, surgery or other painful medical or dental procedure, another group at elevated risk for substance misuse are children and youth with adverse childhood experiences (ACEs), which are potentially traumatic events during childhood and adolescence.[46] A strong association exists between ACEs and an elevated risk of misuse of many types of substances from adolescence into adulthood, suggesting a need for more targeted research on interventions to prevent substance misuse in youth with ACEs.[47,48] Although effective substance misuse prevention interventions for youth exist, the literature calls for patient-centered CER of adapted existing effective prevention programs and approaches to meet the specific individual, interpersonal, and community needs of youth with ACEs.[49,50]

Specific Requirements for This Funding Announcement

To increase evidence that addresses meaningful decisional dilemmas faced by patients, families, clinicians, and other health and health care community members, this funding announcement seeks CER studies that compare interventions across the care continuum to improve patient-centered outcomes in children and youth.

Applicants should provide supportive evidence for the relevance of the treatment options compared and should cite evidence gaps to be addressed that are supported by systematic reviews, guidelines,

or recent research prioritizations.

Population

Proposals should focus on children and youth residing in the United States who are 0 to 24 years old. Applications proposing interventions that involve parents and caregivers are acceptable. Studies that propose to evaluate interventions targeting parents or caregivers that do not include a primary outcome measure of child and youth health or well-being will be considered nonresponsive to the funding announcement.

PCORI is particularly interested in applications focused on underrepresented and/or underresearched populations of youth. Examples are (1) rural-dwelling individuals, (2) individuals with low income, (3) racial and ethnic minorities, (4) individuals with low health literacy and/or limited English proficiency and (5) those living in unstable circumstances. In addition, studies that provide knowledge about an intervention's impact on multiple subgroups (i.e., studies that are adequately powered for evaluating heterogeneity of treatment effects) are strongly encouraged.

Intervention and Comparators

Applicants should propose a study to compare two or more evidence-based interventions (efficacious and/or in widespread use) in which the study results have clear promise to lead to practice change. Applicants should include clear evidence of efficacy that the proposed comparators can improve patient-centered health or well-being outcomes in children and youth. If evidence of efficacy is insufficient, then data should be provided that demonstrate the comparator or intervention is in widespread use.

Applicants may propose comparative effectiveness studies of prevention, screening, diagnostic, treatment, and management approaches and pharmacologic, nonpharmacologic, and/or combination therapies, as appropriate. Studies may also focus on improving system-level strategies delivered in various settings to improve patient-centered outcomes. Multilevel interventions (e.g., organizational, interpersonal, individual) are encouraged. Adaptations (e.g., cultural tailoring) of interventions shown to be efficacious in the general population of children and youth may be responsive, but the level of adaptation must be minimal, clearly described and well justified a priori.

Outcomes

Applicants should propose validated patient, caregiver or clinician-reported outcomes, objective health measures, and/or clinical measures. At least one primary outcome must be a measure of child and youth health and/or well-being. Applicants should propose well-justified outcomes that are clinically meaningful and considered important by patients and that can be affected by the proposed interventions within the study duration.

Time Frame

Depending on the research question, PCORI is interested in both long- and short-term outcomes. When appropriate, applicants are strongly encouraged to consider long-term follow-up periods of 12 months or greater for the primary outcome(s).

Applicants who propose a CER study of an increased study duration (i.e., >5 years and ≤7 years) **must** have a plan for the collection and analysis of longer-term data **at least 24 months from baseline** for at least one primary outcome for all participants. See the Duration of Studies section for further details.

Setting

Clinical, home and community settings, including but not limited to hospitals, outpatient clinics, inpatient rehabilitation services, primary care practices, schools and community-based organizations, are of interest. Other settings are welcomed when selected for their relevance for the specific population of interest. If proposing a clinical setting, the proposed health care setting should be representative of sites where the targeted population typically receives care.

Design

Large randomized controlled trials (RCTs) are preferred; robust observational studies will also be considered with sufficient justification if an RCT is not possible and the proposed approach appropriately controls for confounding. In addition, hybrid effectiveness-implementation studies may be proposed to assist in the translation of research findings into routine practice.[51,52] For this PFA, **one of the primary aims must focus on a comparative clinical effectiveness question**. Hybrid type 1 trials, which have a primary focus on clinical effectiveness outcomes and include a nonprimary implementation aim, and hybrid type 2 trials, which have a dual focus on clinical effectiveness and implementation outcomes, may be appropriate. If such hybrid approaches are used, one of the primary aims must focus on a patient-centered CER question. Hybrid type 3 trials, which focus primarily on implementation outcomes, as well as strict implementation or dissemination studies will not be considered responsive, nor will studies focused on the development of research methods.

PCORI also welcomes rigorously designed studies of natural experiments in patient-centered CER using a population-based approach to assess the impact of clinical interventions that are mediated by policies (e.g., existing state legislative or regulatory policies), systems-level strategies and/or community partnerships. Natural experiments may be particularly well suited to comparing interventions that address social determinants of health by targeting social or economic conditions that can affect health and shape the potential to achieve health equity. Applicants proposing natural experiments must provide justification for how the consequent interventions affect the health status of the target population. Applicants should use strong designs and approaches that adhere to best practices in the field and, when possible, use longitudinal, quasi-experimental designs with concurrent control conditions that adhere to the PCORI Methodology Standards. Applicants must justify study rigor and address potential confounding.[53] Studies should seek to use stable interventions and programs; if the context or policies driving the intervention continue to change, then the risks and benefits of the study should be justified.

Special Areas of Emphasis

Although the funding announcement is open broadly to CER questions that address the health of children and youth, PCORI is particularly interested in submissions that address the following special areas of emphasis (SAEs). The purpose of identifying these SAEs is to encourage submissions to these areas, not to limit submissions to these topics. Applicants who address an SAE should identify the area that is best associated with their research approach.

1. **Prevention and treatment of obesity:** PCORI is interested in comparing evidence-based obesity prevention and treatment approaches for children and adolescents, including dietary, physical activity, lifestyle modification, behavioral, psychosocial, adjunctive pharmacologic or surgical, and/or combination approaches, as appropriate. Studies could include interventions to

improve access to care, quality of care and care navigation involving differences in settings of care, care delivery strategies or use of technology. Interventions may be delivered in the clinical, community and/or school-based setting. Proposed prospective interventional studies should include a multicomponent intervention that uses combination strategies of nutrition, physical activity, or psychosocial support and/or a multilevel intervention that targets individual, family, and sociocontextual factors related to obesity. Robust observational studies or natural experiments examining the comparative effectiveness of various interventions to prevent childhood obesity at the population level that are a result of policies or initiatives that differ across geographies over time (e.g., universal school meals; the Supplemental Nutrition Assistance Program; the Special Supplemental Nutrition Program for Women, Infants, and Children; nutrition standards in school meals; afterschool or in-school physical education) will also be considered. PCORI is especially interested in studies testing evidence-based approaches to equitably implement clinical guideline-recommended care, especially for populations experiencing disparities in outcomes. Studies may include tailoring of intervention strategies as appropriate for the child's developmental age and/or to address cultural characteristics of families. At least one primary outcome should be an obesity-related outcome, such as a recommended child adiposity and anthropometric measurement (e.g., body mass index [BMI] percentile), and is strongly encouraged to be measured for a minimum of 24 months from baseline. Secondary or exploratory outcomes may include but are not limited to dietary quality and intake, physical activity, sedentary time, cardiovascular outcomes, metabolic outcomes, psychosocial outcomes, quality of life, parent BMI, self-efficacy, and weight bias and stigma. Populations disproportionally affected by childhood obesity, including rural, low-income, and racial and ethnic minority groups as well as underresearched populations such as youth with mobility impairments or co-occurring chronic conditions (e.g., asthma, mental health conditions, diabetes, hypertension) are especially of interest.

2. **Addressing social determinants of health and social needs to improve health outcomes:** High-quality CER is needed to test the impact of interventions addressing the social determinants of health (SDOH) and/or social needs (e.g., housing instability and quality, food insecurity) on health outcomes in children and youth. Addressing SDOH and social needs can drive progress toward achieving health equity — one of PCORI's National Priorities for Health. Appropriate interventions of interest to PCORI to address SDOH and social needs include adjustment, assistance and alignment interventions, as defined in the National Academies of Sciences, Engineering, and Medicine committee report *Integrating Social Needs Care Into the Delivery of Health Care to Improve the Nation's Health*.[54] Interventions should be designed to address one or more social needs in the following domains: food insecurity, transportation, housing, education, child care and financial strain. Interventions may be delivered in the clinical and/or community setting (e.g., services delivered by community-based organizations, patient navigators) but must have a link to the health care system. Multicomponent interventions are encouraged, and applicants considering these interventions should refer to the PCORI Methodology Standards for Complex Interventions to ensure that their proposal meets these qualifications. Studies with an intervention arm that solely involves the introduction of a community health worker (CHW) or a patient navigator will be considered nonresponsive; in contrast, studies in which a CHW or patient navigation is embedded in research questions addressing SDOH and social needs and organizational interventions are acceptable. Research teams should strive to partner with public health and/or community-based organizations and should include a study sample that is inclusive of diverse and underrepresented patient

populations. Studies should include a health outcome, such as self- or caregiver-reported physical or mental health status or health-related quality of life, as the primary outcome. Secondary or exploratory outcomes may include but are not limited to SDOH-focused outcomes, such as caregiver employment or improved household food security, or outcomes that demonstrate improvements in health equity. Studies should have a strong plan for sustainability and uptake after the project has been completed.

Examples of responsive projects could include but are not limited to these areas:

- Comparison of the effectiveness of different screening and assistance models for families (e.g., type of screening approach used, type of activities conducted by CHWs or patient navigators, approaches for referral to community resources and follow-up communication)
- Multinetwork observational studies or natural experiments, such as comparisons of the effectiveness of different community programs focused on housing, employment, education or other SDOH, that rely on health system funding and/or leadership and management

3. **Targeted prevention of substance misuse through identified risk factors:** PCORI is interested in patient-centered CER that compares individual-, provider- and/or clinic-level interventions that optimize pain management and reduce risk for sustained prescription opioid use or misuse after injury or trauma (e.g., screening, perioperative pain management education and guidelines). Populations of interest include, but are not limited to, children and youth experiencing pain after injury, surgery or other painful medical or dental procedures. PCORI is also interested in CER studies comparing evidence-based approaches that can prevent substance misuse, SUD or substance use-related harms in children and youth with ACEs or other identified risk factors. Studies should include selective or indicated evidence-based prevention interventions.[55,56] Selective prevention interventions are targeted to individuals with defined risk factors for the development of substance misuse and SUD with the goal of reducing risk and increasing protective factors, whereas indicated prevention strategies are directed at individuals who are experiencing early signs of substance misuse with the goal of halting or slowing the progression of misuse and preventing the development of SUD. Interventions may be delivered in clinical, community, school or virtual settings. Studies may include tailoring of existing, evidence-based prevention models or strategies to meet the needs of the target population (i.e., cultural or age adaptations). Given that some racial and ethnic groups face a disproportionate burden of ACEs,[57,58] culturally tailored or responsive evidence-based interventions that promote equitable health outcomes are highly encouraged. In addition to the groups previously described, applicants may propose studies targeting other groups of children and youth at elevated risk of substance misuse or substance use-related harms due to other identified risk factors (e.g., peer substance use, economic instability, other SDOH), as long as the risk of substance misuse and substance use-related harm and the need for patient-centered CER on prevention approaches in the target population(s) are sufficiently justified. At least one primary outcome should focus on substance misuse. Outcomes that are measured objectively and assessed at least 12 months after baseline are encouraged. Self-reported outcomes should be sufficiently justified. Interventions should be expected to significantly affect the primary outcome(s) within the proposed follow-up period, which may preclude, in prospective studies, the use of some evidence-based prevention strategies focused on young children and/or their families.

Funds Available

PCORI has allotted up to approximately $100 million under this PFA to fund high-quality, patient-centered comparative clinical effectiveness studies that respond to research questions of interest. The proposed budget for studies under this initiative can include up to $12 million in direct costs.

Coverage of Patient Care Costs

Historically, PCORI has not covered the costs for study interventions or the clinical providers who administer them, together termed *patient care costs*. PCORI defines patient care costs broadly to include the cost of interventions themselves (such as medical products, procedures, or care services) and any additional clinical personnel costs associated with administering the interventions. Patient care costs may include procedures, medical devices, diagnostic tools, pharmaceuticals (including drugs and biologicals), and integrative health practices and/or protocols involving clinical providers or other personnel delivering care. Patient care costs may be associated with treatment, care management, and delivery of health care services to treat, manage, diagnose, or prevent illness or injury of individuals.

For this PFA, applicants may participate in a PCORI pilot that allows them to request coverage of patient care costs for *potential* funding by PCORI. This pilot will inform whether allowing such requests can meaningfully expand the breadth and impact of PCORI-funded research. Pilot requests must be realistic, well supported, and justified while satisfactorily addressing the criteria described here. PCORI review and evaluation will determine which, if any, components of requested patient care costs may be potentially fundable. PCORI funding support for patient care costs is not ensured.

By offering the *possibility* of funding support for patient care costs, PCORI intends to minimize financial hardship and barriers for patients and/or institutions to participate in *critically important* comparative effectiveness research. Note that PCORI is not seeking to equalize insurance coverage or compensation to medical providers and institutions.

Although PCORI will consider and review requests for coverage of patient care costs, researchers are encouraged to seek funding or cofunding from a third party. Cost sharing by a third party (to provide a product, service, or other coverage) can provide evidence of support for a study and can demonstrate an increased likelihood for future sustainability and uptake of results.

The criteria for justification to be captured in the full application are as follows:

- Does the study address a strategically important comparative effectiveness question? For example, does it address a comparative effectiveness question identified by a systematic review or related to PCORI's Topic Themes? Would study results have a potentially significant impact on clinical decision making or policy formation because of a major therapeutic advance in a medical product, procedure, or care delivery innovation?
- Does evidence show that the absence of coverage of patient care costs will pose a significant barrier to adequate recruitment of participants or to the access or inclusion of key participant groups? Would a significant and impactful research project be otherwise impossible to conduct without coverage of patient care costs?
- Is there a high likelihood of sustained uptake of study results in the absence of future cost subsidies, as evidenced by key stakeholders who have committed in letters of support to provide future support of patient care costs through staffing, reimbursement of services, modified policies, or other actions? Have any stakeholders evidenced their good-faith

support of future implementation of the intervention(s) through contributions of funding or resources (e.g., data, personnel or a portion of personnel time, infrastructure, other in-kind items) to offset and reduce patient care costs requested of PCORI?

Applications are permitted to request PCORI coverage for patient care costs but must remain within the $12 million direct cost maximum.

Like all funding requests, the extent and amount of PCORI funding will be resolved in the process of contract and budget negotiations with applications chosen for award. Applicants should be prepared to address contingencies for conducting the proposed study if PCORI declines to pay for some or all of the requested patient care costs.

Investigators seeking coverage of patient care costs should note such requests when submitting LOIs to this PFA (as indicated in the LOI template). Invited applications should describe the patient care costs, their estimated amount(s), and the evidence and justification for their funding by addressing these criteria within the appropriate sections of the application, described further in the Submission Instructions.

Duration of Studies

The funding announcement's standard maximum project period is five years (60 months). PCORI expects that most proposals responding to this funding announcement will be less than or equal to five years in duration to provide timely study results that inform health decisions. *In exceptional circumstances*, PCORI will consider applications that propose projects up to seven years in duration, with strong justification, provided that they aim to assess longer-term outcomes, and demonstrate that the proposed study duration is critical to answering the proposed CER question. Such applications must have a plan for the collection and analysis of longer-term data at least 24 months from baseline for at least one primary outcome for all participants as well as a compelling rationale for why the primary outcome(s) would benefit from and/or require that length of follow-up.

Applicants are strongly encouraged to discuss such a request to exceed the 5-year maximum project period with PCORI prior to submission of a Letter of Intent (LOI). Applicants who are requesting PCORI review for an increased study duration (i.e., >5 years and ≤7 years) must complete the separate addendum "Request for Increased Study Duration" of the LOI template. This addendum is limited to one page and will not be included in the LOI three-page limit. Requests to exceed the maximum project period will be reviewed with the submitted LOI. PCORI approval of an increased study duration is required at the LOI stage before application submission. Applications that exceed the five-year maximum project period without prior PCORI approval will be administratively withdrawn and not forwarded for further review.

II. General Requirements for PCORI Research

This section includes language that is specific to PCORI's requirements for programmatic responsiveness under this funding announcement. Applicants should use this section as guidance when preparing their applications. For information related to administrative and technical requirements for Letter of Intent (LOI) and application submission, consult the Submission Instructions.

Patient and Stakeholder Engagement

In PCORI-funded research, patients and other health care stakeholders are expected to be integrated as partners who leverage their lived experience and/or professional expertise to influence research to be more patient-centered, relevant, and useful to patients and providers in making health care decisions. In 2024 PCORI launched updated engagement guidance titled Engagement in Research: Foundational Expectations for Partnerships. The Foundational Expectations for Partnerships provide a systematic framework for patient and stakeholder engagement that is firmly built on prior evidence. PCORI has developed or identified tools and resources to support research teams designing their engagement strategies in alignment with these Foundational Expectations.

The Foundational Expectations are building blocks for meaningful, effective, and sustainable engagement with patients, communities, and other partners in research. Applicants are required to provide an overview of their engagement approach that demonstrates how the Foundational Expectations were addressed in their engagement plans. Addressing the Foundational Expectations for Partnerships in Research is a **requirement** for PCORI applicants. Details on each of the Foundational Expectations are available at (www.pcori.org/Foundational-Expectations). When developing an engagement strategy, applicants **must address** the following expectations:

1. Diversity & Representation
2. Early & Ongoing Engagement
3. Dedicated Funds for Engagement & Partner Compensation
4. Build Capacity to Work as a Team
5. Meaningful Inclusion of Partners in Decision Making
6. Ongoing Review of Assessment of Engagement

Applicants should use multiple approaches that occur along a continuum of engagement—from input to shared leadership.[59] For example, study teams may find it useful to solicit input from a large group of stakeholders using quick-turnaround methods (e.g., focus groups, surveys, crowdsourcing, virtual or in-person roundtables, community forums) in addition to engaging stakeholders via ongoing consultative groups (e.g., advisory committees, working groups), collaborative arrangements, and leadership positions (e.g., co-investigators, multidisciplinary steering committees) that are sustained throughout the study. While engagement approaches that solicit input (e.g., focus groups, surveys, crowdsourcing, virtual or in-person roundtables, community forums) can be utilized if appropriate, note that ONLY soliciting input would not be considered meaningful engagement and would be considered nonresponsive.

Applicants should provide an overview of their engagement approach that demonstrates that they have addressed the Foundational Expectations. This should include a proposed list of patient and other health care research partners (include names and affiliations, if available), the perspectives they will represent, and rationale for their inclusion; the goals for working with stakeholders, which may include effects on the acceptability, feasibility, rigor, and/or relevance of the study; and a description of how the team will engage with stakeholders at key decision points throughout the study. Assessment of engagement activities is a required component of the engagement overview, which should also address plans to learn about what is working well and what could be improved, to allow for adjustments to engagement approaches as needed.

Applicants should also budget for engagement and ensure that the budget narrative clearly identifies the funds to be allocated for engagement activities, personnel and partner compensation.

Funded awardees are required to submit a more detailed engagement plan six months after contract execution.

Engagement strategies should be guided by PCORI's Foundational Expectations for Partnerships in Research. Additional engagement resources are also available on PCORI's website.

Research Requirements

To be considered responsive, applications must do the following:

- ***Describe comparators.*** Regardless of the approach being studied, all proposed research projects must compare at least two alternatives. If the applicant proposes *usual care* as a rational and important comparator in the proposed study, then it must be described in detail, coherent as a clinical alternative, and properly justified as a legitimate comparator. The choice of usual care must represent current clinical and ethical standards of care. It must also be accompanied by an explanation of how the care given in the usual care group will be measured in each patient and how appropriate inferences will be drawn from its inclusion. Usual care must be described as mentioned above to ensure that it accounts for geographic and temporal variations and that it has wide interpretability, applicability, and reproducibility. See Standards for Usual Care as a Comparator within *Cross-Cutting Standards for Patient-Centered CER.*
- ***Describe research that compares two or more alternatives, each of which has established efficacy and/or is in widespread use.*** PCORI expects the efficacy or effectiveness of each intervention to be known. If the efficacy or evidence base is insufficient, then data must be provided to document that the intervention is used widely. The application must provide information about the efficacy of the interventions that will be compared; pilot data might be appropriate. Projects aiming to develop new interventions that lack evidence of efficacy, effectiveness, or widespread use will be considered out of scope.
- ***Describe research that studies the benefits and harms of interventions and strategies delivered in real-world settings.*** PCORI is interested in studies that provide practical information that can help patients and members of the broader health and health care community make informed decisions about their health care and health outcomes.
- ***Describe consultation with patients and members of the broader health and health care community about how the study is answering a critical question.*** PCORI expects applicants to explain the pertinent evidence gaps and why the project questions represent decisional dilemmas for patients, caregivers, clinicians, policy makers, and other health care system stakeholders. Describe why project outcomes are especially relevant and meaningful endpoints to patients and members of the broader health and health care community.

Responsiveness Review

PCORI conducts rigorous review of the LOIs and applications it receives. Note that PCORI may withdraw LOIs or applications from the review process for administrative or programmatic reasons (e.g., nonresponsiveness or other administrative or programmatic reasons). An LOI or application may be administratively withdrawn if it is incomplete; is submitted past the stated due date and time; has an application budget of more than the budget limits as specified in this PFA; or does not meet the formatting criteria outlined in the Submission Instructions, in the PCORI templates, and in PCORI Online. An LOI or application may be withdrawn for programmatic nonresponsiveness if it

does not address the specifications described in this PFA, describes research that is not comparative, includes a cost-effectiveness analysis of alternative approaches to providing care, or otherwise does not meet PCORI programmatic requirements. PCORI may also consider withdrawing an LOI or application for administrative and/or programmatic reasons if PCORI is evaluating or reviewing an "Allegation of Research Misconduct" or there is a finding of Research Misconduct relating to the LOI or application, consistent with PCORI's Research Misconduct Policy.

Categories of Nonresponsiveness

PCORI discourages applications in the following categories and will deem them nonresponsive:

- Development of instruments, such as new surveys or scales
- Development, testing, and validation of new decision aids and tools or clinical prognostication tools
- Pilot studies intended to inform larger efforts
- Comparison of patient characteristics rather than clinical strategy options
- Studies where the intervention arm is limited solely to the addition of a community health worker or patient navigator
- Studies designed to test the efficacy of unproven interventions
- Studies whose principal focus is on quality improvement
- Studies that propose to develop and compare new health policies or programs
- Studies whose exclusive focus is on stakeholder engagement
- Studies whose exclusive focus is on disseminating an intervention without any research comparison
- Studies that propose only input approaches to engagement

Consistent with PCORI's authorizing law,[60] PCORI does not fund research for which findings will include the following:

- Coverage recommendations
- Payment or policy recommendations
- Creation of clinical practice guidelines or clinical pathways
- Establishment of efficacy for a new clinical strategy
- Pharmacodynamics
- Study of the natural history of disease
- Basic science or the study of biological mechanisms

Further, PCORI will also consider an application nonresponsive if the proposed research:

- 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

- Relies on cost simulation modeling to develop estimates of total costs of care beyond the scope and time horizon of the study

Consideration of Full Range of Outcomes Data in PCORI-Funded Research

PCORI's authorizing law states that PCORI-funded research shall consider, as appropriate, the full range of clinical and patient-centered outcomes data that are relevant and important to patients and members of the broader health and health care community. In addition to health outcomes and clinical effectiveness, relevant outcomes within PCORI-funded projects may include the potential burdens and economic impacts of the utilization of medical treatments, items, and services when relevant to patients and caregivers or to members of the broader health and health care community.

PCORI's intention is that PCORI-funded research will capture such burdens and economic impacts, when germane, to provide the full range of outcomes data relevant to decision-makers.

In March 2021, PCORI's Board of Governors approved Principles for the Consideration of the Full Range of Outcomes Data in PCORI-Funded Research. These principles inform PCORI's expectations for applicants and the corresponding evaluation of applications submitted in response to this PFA.

Applicants should note the following important points related to the capture of the full range of outcomes data:

- PCORI encourages all investigators to identify, collect data on, and describe the full range of patient-centered and clinical outcomes relevant to patients and members of the broader health and health care community. These outcomes can include relevant costs and other burdens. In their application, and where applicable, investigators should outline the relevance of the cost or other burdens they will examine in their proposed research.
- PCORI's intention in the collection of the full range of outcomes data is to leverage researchers' knowledge of and ability to obtain data relevant and linked to the primary clinical effectiveness outcomes of their research. As such, with respect to costs and other burdens, investigators should not focus on cost analysis but on collecting and summarizing data. If cost and economic burden data are collected, then PCORI expects investigators to provide descriptive summaries of these data—in addition to the primary and other secondary outcomes collected as part of the study—in the Final Research Report. These estimates may serve as inputs to support decision makers and others in conducting their own analyses to support specific decisions.
- As outlined in Principles for the Consideration of the Full Range of Outcomes Data in PCORI-Funded Research, PCORI will not fund studies
    - For which costs and economic impacts are the primary outcomes.
    - That develop or employ dollars-per-quality-adjusted life year (QALY) or similar adjusted life year thresholds
    - That mandates coverage, reimbursement or other policies for any public or private payer, or makes practice guidelines, coverage recommendations, payment or policy recommendations
- Relatedly, simulation modeling efforts, which generate estimates of cost that extend beyond the data collected, are outside PCORI's scope of interest. PCORI research awards will not

support such cost modeling activities.

- As part of its interpretation of the authorizing law, PCORI will not fund studies that develop or employ QALYs or similar adjusted life year outcomes.

PCORI focuses its funded research studies on comparative clinical effectiveness. While PCORI is committed to expanding the range of outcomes to be collected, the prohibition remains on cost-effectiveness analysis. To ensure compliance with the spirit as well as the language of this prohibition, PCORI does not allow analyses in which the cost of care could be interpreted as driving the choice of interventions. Cost may be one consideration in the choice of interventions, but it will generally not be the only one or even the most important. For example, patient-centered considerations such as the convenience of dosing or individual preference, or the availability of relevant personnel for delivering an intervention, may influence decision making.

Analyses that focus on a cost comparison to determine (or that could be interpreted as determining) a preferred intervention will be interpreted by PCORI as intention to perform cost-effectiveness analysis and considered nonresponsive. Therefore, although investigators may collect a wide range of data and present the total costs of an intervention and its outcomes, these analyses may only be descriptive. The PCORI award must focus on comparisons of the effectiveness outcomes and should not present direct comparisons of total costs of care.

While comparisons of total cost of care are prohibited, comparison of subcategory of total costs of care reflecting burdens, costs, and other economic impacts on patients and caregivers are permissible; however, they should still not be done with the intent to affect coverage, reimbursement or other policies for any public or private payer, or make practice guidelines, coverage recommendations, payment or policy recommendations.

A landscape document of potential examples of patient-centered burdens and economic outcomes that PCORI encourages applicants to consider can be found here. These outcomes cannot be the primary outcomes of the study, but they may be secondary outcomes and they may be directly compared.

For further information regarding PCORI's policies on potential burdens, costs, and other economic impacts, reference PCORI's cost and economic burdens FAQs.

PCORI Methodology Standards: Methodological Requirements and Considerations

PCORI's authorizing law requires all proposed studies to adhere to the PCORI Methodology Standards, which 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 must be justified. Applicants should address additional best practices—including relevant guidelines for conducting clinical trials developed by other organizations—in the application for PCORI funding.

PCORI expects applicants to fully implement the PCORI Methodology Standards and methodological best practices across all study phases to ensure the conduct of scientifically valid, comparative clinical effectiveness research, and to budget appropriately for these activities. In some circumstances, it may be appropriate to implement advanced methodologies (e.g., study design, modeling, or analytic approaches supported by the PCORI Improving Methods portfolio) to provide sophisticated solutions to statistical/data challenges in CER.

Patient-Centered Outcome Measures

PCORI encourages investigators to design their research using validated outcome measures and to include preliminary data that support using the proposed measures in the study population. PCORI encourages investigators to consider measures such as those described in the PROMIS® (Patient-Reported Outcomes Measurement Information System)[36] and core outcome sets, such as those developed by the COMET® (Core Outcomes Measures in Effectiveness Trials Initiative), to facilitate cross-study analysis.

Leveraging Existing Resources, Including PCORnet®

PCORI encourages applicants to consider the potential merits of using the clinical research infrastructure, including engagement and data resources available through PCORnet. PCORnet is a national resource, funded by PCORI, where high-quality health data, patient partnership, and research expertise deliver fast, trustworthy answers that advance health outcomes by drawing on a network of patient partners, clinicians, and Clinical Research Networks (CRNs). PCORnet is a national resource accessible to all investigators through the PCORnet Front Door.

PCORnet facilitates access to electronic health record data for research, including encounters from more than 30 million patients across the United States. This "network of networks" includes a diverse range of over 13,000 clinical care sites, communities, and patient populations and demographics that are comparable to the US population.[61] PCORnet investigators, patients, and stakeholder engagement teams have deep experience in conducting a range of study designs that include meaningful stakeholder engagement. The PCORnet infrastructure is unique in that its distributed structure and Common Data Model permit direct connections to patients and providers and access of primary data with appropriate privacy and confidentiality protections consistent with legal requirements.

PCORnet infrastructure offers the following resources to researchers interested in using PCORnet to support both interventional and observational research:

- Clinical Research Networks that can participate as clinical sites in randomized research trials
- Actively engaged patients, clinicians, and health systems

PCORnet infrastructure offers the following resources to researchers interested in using PCORnet to support both interventional and observational research:

- Clinical Research Networks that can participate as clinical sites in randomized research trials
- Actively engaged patients, clinicians, and health systems
- Preexisting, standardized, curated, and research-ready clinical data on clinical outcomes and details of specific procedures, treatments, disease severity, and comorbid illnesses through the PCORnet Common Data Model (CDM) (more details available at https://pcornet.org/data/)
- Support for trial design and feasibility assessments and to inform study power calculations

Applicants interested in engaging with PCORnet and using the resources available through PCORnet are encouraged to contact the PCORnet Front Door as soon as possible, ideally before LOI submission, to learn more and explore opportunities to use PCORnet resources. If applicants have contacted the Front Door, they should provide a Front Door number, provided as part of the Front Door consultation, in the submitted LOI.

Diversity in Populations Studied and Recruited

To promote inclusivity and equity in the benefit achieved through research findings, 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 outcomes may be examined in defined subpopulations. PCORI recognizes that some proposed research projects might represent important patient-centered CER opportunities even in the absence of a diverse study population, but at a minimum, the expectation is that the study population reflect the diversity of those affected by the condition(s) of focus. However, the burden is on the applicant to justify the importance of the proposed research project 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 relative effectiveness among subgroups.

PCORI seeks to fund projects that reflect the principles of equity, diversity, and inclusion and is particularly interested in research projects designed to recruit and retain previously understudied populations for whom information on clinical effectiveness is especially needed, such as populations not traditionally included in research, populations, or patients without ready access to health care, or patients with multiple health 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 its efforts in research and engagement:

- Underrepresented racial and ethnic minority groups*
- Low-income groups*
- Women
- Children (ages 0–17 years)
- Older adults (ages 65 years and older)
- Residents of rural areas*
- Individuals with special health care 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 US Armed Forces and their families

*These groups are identified as populations of interest for the National Priorities for Health goal: Achieve Health Equity.

Regardless of the population studied, investigators are expected to provide evidence-based estimates regarding the representativeness of the potential pool of participants from which recruitment will occur, the target sample size, and recruitment and retention rates reflecting the study's inclusion and exclusion criteria as well as factors that may affect the final sample size (e.g., loss to follow-up).

Protection of Human Subjects

PCORI-funded research projects are expected to follow the Federal Regulation for the Protection of Human Subjects (45 C.F.R. § 46), including the Common Rule. If the research project involves human subjects as defined by federal regulations at 45 C.F.R. § 46.102, awardees must ensure that an institutional review board provides initial and continuing review and approval of the research project. Awardees must also comply with applicable state, local, and institutional regulations and guidelines pertaining to the use of human subjects in research, including any privacy concerns (see below). The Awardee Institution bears ultimate responsibility for safeguarding the rights and welfare of human subjects in PCORI-funded research projects.

PCORI requires awardees to ensure there is a Data and Safety Monitoring Plan, which may require the appointment of a Data and Safety Monitoring Board, as provided in the PCORI Policy on Data and Safety Monitoring Plans for PCORI-Funded Research.

PCORI will consider the human subject protection plan for all applications (see How to Evaluate Human Subjects Protections). However, this consideration does not contribute to the overall score for an application. The institutional review board, or international equivalent, that has jurisdiction for the proposed study makes the final determination of the adequacy of the human subjects protection plan.

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

PCORI requires that all awardees 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.[62]

Standards for Privacy of Individually Identifiable Health Information

PCORI-funded activities are expected to comply with applicable federal, state, and local laws and regulations of any applicable jurisdiction governing the privacy and security of health information, including, if applicable, the Health Insurance Portability and Accountability Act (HIPAA) and its implementing regulations. Resources and tools on specific requirements may be available through federal or state sources; PCORI encourages institutions to consult such resources for more information as appropriate.

III. LOI Review

Applying for funding for this PFA 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 the priority research question for this Topical PFA, as evidenced by critical gaps identified by stakeholders, clinical guidelines developers and/or recent systematic reviews
- Clarity and credibility of responses to the LOI questions and compliance with PFA

requirements

- Sufficient detail and scientific rigor of the proposed methods
- Clarity and credibility of proposed engagement activities with patients, communities and other partners
- 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 unique characteristics, including disease category, topics, priority population, methodologies, and other variables
- Prior acceptance of an LOI or application does not guarantee acceptance of future LOIs on the same topic. LOIs that are resubmissions are expected to incorporate modifications related to major weaknesses noted in prior review

Only applicants whose LOIs are deemed most responsive to this PFA will be invited to submit a full application.

Please note: To protect the confidentiality of LOI and application information, PCORI prohibits the sharing, uploading, or providing Confidential Information through the use of technological tools such as generative artificial intelligence (AI) in its competitive funding review processes.

IV. Merit Review

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

- Identify applications that have the strongest potential to help patients, caregivers, clinicians, policy makers, and other health care system stakeholders make informed decisions to improve patient outcomes.
- Implement a transparent, fair, objective, and consistent process to identify these applications.
- Identify projects that fill important evidence gaps and have strong implementation potential.

PCORI merit review is a two-stage process that includes an initial preliminary review of full applications by individual review panel members and a subsequent panel discussion of a subset of competitive applications.

Please note: To protect the confidentiality of LOI and application information, PCORI prohibits the sharing, uploading, or providing Confidential Information through the use of technological tools such as generative artificial intelligence (AI) in its competitive funding review processes.

Review Criteria

Applications are evaluated on the following review criteria:

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

An evidence gap is an area of missing information that would help patients and members of the broader health and health care community make better decisions about health care. The application

should clearly justify the importance of the clinical or care delivery problems that the study will address and whether the proposed approach is appropriately conceptualized.

The application should address the following questions:

- Does the application convincingly describe the clinical burden?
- Does the application identify a critical gap in current knowledge as noted in systematic reviews, guideline development efforts, and/or authoritative recommendations by stakeholder organizations? Is there evidence of inconsistency in clinical practice and decision making? If the proposal has an increased study duration (i.e., >5 years and ≤ 7 years) to evaluate longer-term outcomes, does the application cite an evidence gap specific to longer-term outcomes?
- If the aims of the proposed study are achieved, would research findings have the potential to fill the demonstrated evidence gaps?

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

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

- Does the application identify local and/or national end users who have expressed their interest in applying study findings?
- Would the study's findings inform decision making for end users? If the proposal has an increased study duration (i.e., >5 years and ≤ 7 years) to evaluate longer-term outcomes, does the application provide information that supports a demand for evaluating long-term outcomes from end-users?
- Has the applicant identified potential barriers to intervention adoption and strategies to address such barriers?
- Has the applicant identified resources or factors that would promote adoption of the intervention?

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

The application should show sufficient scientific merit in the Research Plan to ensure that the study goals will be met. The application should address the following questions:

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

appropriate for the population?

- Are each of the comparators described clearly and well justified with appropriate evidence supporting their efficacy and/or widespread use? If "usual care" is one of the arms, is it adequately described and justified, and will it be sufficiently measured?
- Are sample sizes and power estimates well justified and appropriate for the proposed study design and research question? Is the anticipated effect size adequately justified?
- Is the Research Plan feasible? For example:
  - Are the project timeline and milestones realistic?
  - Is the strategy for recruiting participants feasible?
  - Are assumptions about participant and/or site attrition realistic, and are plans to address attrition adequate?
  - If the proposal has an increased study duration (i.e., >5 years and ≤ 7 years) to evaluate longer-term outcomes, is the strategy for data collection and maintaining contact with participants over time feasible? Are assumptions about participant attrition for long-term outcomes realistic, and are plans to address patient or site attrition adequate?

Criterion 4. Investigator(s) and environment

The application should demonstrate how well prepared the principal investigators (PIs) and other members of the study team are to conduct the proposed activities and the environment's capacity to support the proposed project. Assessment of this criterion should not focus on the institution's reputation but rather on the breadth and depth of available institutional personnel and resources. The application should address the following questions:

- Do members of the study team have complementary and integrated expertise? Is there evidence of sufficient clinical, statistical, and study management expertise?
- Do investigators have experience conducting projects of a similar study design, size, scope, and complexity?
- Are the leadership, governance, and organizational structures of the study team clear and appropriate for the project? For Dual-PI applications, does the Leadership Plan adequately describe and justify PI roles and areas of responsibility?
- Does the application describe adequate availability of and access to facilities and resources for the proposed research?
- Is the institutional support appropriate for the proposed research?

Criterion 5. Patient centeredness

The application should demonstrate that the study focuses on improving patient-centered outcomes and employs a patient-centered research design—that is, 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 address the following questions:

- Does the application include a thorough description about which outcomes are important to

patients, and are those outcomes included in the Research Plan? If the proposal has an increased study duration (i.e., >5 years and ≤ 7 years) to evaluate longer-term outcomes, does the application include a thorough description that longer-term outcomes are important to patients and other stakeholders?

- Does the application provide information that indicates that closing the evidence gap is important to patients and other stakeholders?
- Does the application present evidence of patients' willingness to accept the proposed comparators considering their potential benefits, risks, and burdens of time, inconvenience, out-of-pocket costs, and other factors?

Criterion 6. Patient and stakeholder engagement

The application should demonstrate that the Foundational Expectations for Partnerships in Research were addressed, including engaging relevant patients and members of the broader health and health care community in the conduct of the proposed study. Applicants should include engagement approaches that are appropriate and tailored to the study while addressing the specific goals and needs of their proposed study. The application should address the following questions related to the individual Foundational Expectations:

- **Diversity and Representation:** Does the application show evidence of including partners, organizations, researchers, and other team members who reflect the diversity of patients and communities affected by the research topic?
- **Early and Ongoing Engagement:** Does the application provide a well-justified description of how the partners will contribute early and throughout all the phases of the study?
- **Dedicated Funds for Engagement and Compensation of Partners:** Does the application plan to equitably allocate sufficient resources for engagement and partner compensation?
- **Build Capacity to Work as a Team:** Does the application include plans to ensure the study's team and partners are ready to engage by building on and strengthening partner skills, and addressing barriers to engagement?
- **Meaningful Inclusion of Partners in Decision-Making:** Does the application describe how engagement will support inclusion of partners in decision making throughout all phases of the study (from design to conduct to interpretation and dissemination of results), in alignment with study goals, scope and scale?
- **Ongoing Review and Assessment of Engagement:** Does the application include plans to gather input and feedback to identify opportunities to improve engagement throughout the project period?

Additional Review Considerations

There are no additional requirements.

Merit Review Process

For the initial stage of merit review, applications are evaluated by a set of five or more reviewers who provide written critiques that address the merit review criteria and any additional review considerations. Each application receives review evaluation by scientists, patients, and stakeholders,

who have complementary expertise and perspectives. Scientist reviewers represent the perspectives of subject matter experts, methodologists, and generalists/clinical trialists. Patient reviewers represent the perspective of individuals who are recipients of the proposed health care intervention. Stakeholder reviewers represent the perspective of providers, administrators, and payers of the proposed health care intervention. For the second stage of merit review, competitive applications proceed to a review panel meeting where applications are discussed by the full set of all panel reviewers who do not have a known conflict of interest with an application.

Summary Statements

All applications determined to be responsive to PCORI program requirements receive a summary statement with written critiques from the first stage merit review. If an application progresses to the discussion stage, the summary statement will also include the following:

- Panel discussion notes
- Final average overall score

Summary statements are provided to applicants when funding decisions are announced.

V. Programmatic Review, Recommendations, and Award Approval

After the merit review meeting, PCORI evaluates final merit review panel scores and comments, assembles a list of recommended projects for each funding announcement, and reviews projects to ensure organizational and programmatic alignment.

In some circumstances, PCORI may have questions that must be addressed before the application can be recommended for funding. Common questions include ability to meet study milestones according to the proposed timeline, methodological issues raised during merit review or methodology consults, meaningful engagement of patients and other stakeholders, and reasonableness of the proposed budget and personnel effort. During the PCORI Information Request (PIR) phase of the process, PCORI may send the applicant a list of questions and concerns for response by a given deadline, typically within two weeks. Applicant responses to PIRs are carefully reviewed to inform funding recommendations. PCORI may repeat this process as needed. Submission of a PIR response does not guarantee that the application will be recommended for funding.

PCORI will take the following criteria into consideration to make funding recommendations and select applications that, individually or collectively, will best achieve the program objectives:

- Ratings and evaluations of the merit reviewers
- Relevance to PCORI's research agenda
- Compliance with programmatic requirements of the PCORI Funding Announcement
- Satisfactory response to PIR questions and concerns
- Whether the proposed project overlaps, or has synergy with, research described in other applications being considered for funding or already funded projects

- Satisfactory engagement within the proposed project consistent with the Foundational Expectations for Partnerships in Research
- Relative impact and innovation

PCORI then recommends a slate of applications to either the Standing Selection Committee or a Special Selection Committee, both comprised of members of the Board of Governors and other individuals appropriate to the funding opportunities under review. The committee considers whether the slate is aligned with PCORI's strategic priorities, and then advances a final slate to the PCORI Executive Director for consideration and approval of award funding in accordance with funds available under PCORI's Board-approved Commitment Plan.

Please note: To protect the confidentiality of LOI and application information, PCORI prohibits the sharing, uploading, or providing Confidential Information through the use of technological tools such as generative artificial intelligence (AI) in its competitive funding review processes.

VI. PCORI Policies That Govern Research Project Awardees Related to Data Sharing, Peer Review and Findings Release, and Public Reporting

Applicants should be aware that all PCORI research project awardees are required to comply with several policies, including the policies referenced here. Visit the Applicant Resources section and Policies & Guidelines pages at www.PCORI.org for additional details.

Registering Research Projects

All research projects that meet the definition of clinical trials on the NIH database (see Data Element Definitions) are required to register with ClinicalTrials.gov, if funded. Research projects that do not meet the definition of clinical trials may be required to register the research project at another appropriate site for the study design.

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.

Policy for Data Management and Data Sharing

PCORI is committed to the principles of open science, particularly maximizing the utility and usability of data collected in research projects that PCORI funds. PCORI encourages scientifically rigorous secondary use of clinical research data to foster scientific advances that ultimately improve clinical care and patient outcomes. As such, PCORI believes it is important for research project awardees to systematically create and preserve research data and data documentation to facilitate data sharing. All research project awardees must agree to these principles and take steps set forth in the Policy for Data Management and Data Sharing.

PCORI encourages making research data available for purposes of replication and reproducibility. As such, **all** awardees funded through this PFA will be expected to adhere to PCORI's Policy for Data Management and Data Sharing. This policy also articulates PCORI's requirement that awardees make the underlying data and data documentation (e.g., study protocol, metadata, and 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 Data Management and Data Sharing Policy includes details about what data awardees will be expected to deposit into a PCORI-designated data repository and when those data would be available for third-party requests.

Consistent with PCORI's Policy for Data Management and Data Sharing, PCORI intends to provide funds for the deposition of the Full Data Package to a PCORI-designated repository. This notice is provided because of PCORI's estimation of the high importance of and interest in findings from research projects funded under this PFA.

The information here 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.

PCORI's Process for Peer Review of Primary Research and Public Release of Research Findings

Consistent with the requirements of PCORI's authorizing law and PCORI's Process for Peer Review of Primary Research and Public Release of Research Findings, awardee institutions are required to submit to PCORI for peer review a draft of the final research report that describes the main research project results, provides the methodological details, and interprets the findings in clinical or other decisional contexts. PCORI will conduct peer review of the draft final research report to determine whether the evidence and analyses support the conclusions of the report and whether the study methods adhere to PCORI's Methodology Standards. After peer review, PCORI works with awardee institutions to make research project findings available on PCORI's website, including for patients and professionals, and with conflict-of-interest reporting.

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