



Spring 2015 Funding Cycle

PCORI Funding Announcement: Clinical Management of Hepatitis C Infection

Published February 4, 2015

This PCORI Funding Announcement applies to the funding cycle that closes on May 5, 2015, at 5:00 p.m. (ET). Application guidelines, templates, and other resources are available at <http://www.pcori.org/announcement/hepatitis-c>.



About PCORI

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

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

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Overview

Published	February 4, 2015																
Letter of Intent Due	March 6, 2015, by 5:00 p.m. (ET)																
Summary	<p>Letters of Intent (LOIs) will be screened for responsiveness to this PCORI Funding Announcement (PFA) and fit to program goals. Only those applicants selected will be permitted to submit full applications. Notification of denial or approval to submit a full application will occur no later than March 23, 2015.</p> <p>The Patient-Centered Outcomes Research Institute (PCORI) seeks to fund pragmatic clinical trials (PCTs), or observational studies that compare two or more alternatives for addressing diagnosis, treatment, or management of hepatitis C infection. The research is expected to examine treatment options as well as systems-level interventions or those aimed at eliminating health or healthcare disparities.</p> <p>Proposed studies must address clinical and healthcare delivery choices faced by patients, their caregivers, clinicians, and/or delivery systems. Proposed studies must compare two or more active interventions. They must involve patient populations that are representative of the US population and be large enough to provide precise estimates of hypothesized effectiveness differences and to support evaluation of potential differences in treatment effectiveness in patient subgroups.</p> <p>For this solicitation, relevant patient organizations, professional organizations, payer or purchaser organizations, and/or manufacturers must be included as partners and active participants in developing the application and carrying out the research. PCORI expects most applications to propose study designs that use randomization, either of individual participants or clusters, to avoid bias due to confounding. However, we encourage investigators who identify exceptional opportunities, by virtue of natural experiments and/or the existence of large registries, to use observational designs to address the research questions. Note that this funding program does not support applications to conduct cost-effectiveness analysis, systematic reviews, or development and/or evaluations of shared decision-making or decision-support tools.</p> <p>The proposed studies must address at least one of the four priority research questions identified in the main body of the PFA.</p>																
Applicant Resources	See http://www.pcori.org/announcement/hepatitis-c																
Key Dates	<table><tr><td>Online System Opens:</td><td>February 4, 2015</td></tr><tr><td>Applicant Town Hall Session:</td><td>February 11, 2015, 11:00 a.m. – 12:30 p.m. (ET)</td></tr><tr><td>Letter of Intent (LOI) Deadline:</td><td>March 6, 2015, by 5:00 p.m. (ET)</td></tr><tr><td>Screening Notification:</td><td>March 23, 2015</td></tr><tr><td>Application Deadline:</td><td>May 5, 2015, by 5:00 p.m. (ET)</td></tr><tr><td>Merit Review Dates:</td><td>August 6–7, 2015</td></tr><tr><td>Awards Announced:</td><td>September 2015</td></tr><tr><td>Earliest Project Start Date:</td><td>November 2015</td></tr></table>	Online System Opens:	February 4, 2015	Applicant Town Hall Session:	February 11, 2015, 11:00 a.m. – 12:30 p.m. (ET)	Letter of Intent (LOI) Deadline:	March 6, 2015, by 5:00 p.m. (ET)	Screening Notification:	March 23, 2015	Application Deadline:	May 5, 2015, by 5:00 p.m. (ET)	Merit Review Dates:	August 6–7, 2015	Awards Announced:	September 2015	Earliest Project Start Date:	November 2015
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Earliest Project Start Date:	November 2015																
Maximum Project Budget (Total Direct Costs)	\$20 million																



Maximum Project Period	5 years
Funds Available Up To	\$50 million
Eligibility	Applications may be submitted by any private-sector research organization, including any nonprofit or for-profit organization; any public sector research organization, including any university or college hospital or healthcare system, laboratory, or manufacturer; or unit of local, state, or federal government. All US applicant organizations must be recognized by the Internal Revenue Service. Nondomestic components of organizations based in the United States and foreign organizations may apply as long as there is demonstrable benefit to the US healthcare system and US efforts in the area of patient-centered research can be clearly shown. Organizations may submit multiple applications for funding. Individuals are not permitted to apply.
Review Criteria	<ol style="list-style-type: none">1. Impact and importance of the research aims, interventions, comparators, and outcomes on individuals with hepatitis C and their caregivers, clinicians, employers, insurers, and policy makers2. Potential for the study results to be incorporated into clinical practice3. Technical merit4. Patient-centeredness5. Patient and stakeholder engagement
Contact Us	<p>Programmatic Inquiries: Contact the PCORI Helpdesk via email (sciencequestions@pcori.org), phone (202-627-1884), or complete the Research Inquiry Form (http://www.pcori.org/content/research-inquiry). PCORI will provide a response within three business days. However, we cannot guarantee that all questions will be addressed in a timely fashion when the inquiry is made three or fewer business days prior to an LOI or application deadline.</p> <p>Administrative, Financial, or Technical Inquiries: Contact the PCORI Helpdesk at pfa@pcori.org. PCORI will provide a response within two business days. Note that during the week of the application deadline, response times may exceed two business days. One week prior to an application deadline, applicants may also call the PCORI Helpdesk (202-627-1885). Applicants are asked to plan accordingly. It is the applicant's responsibility to submit the application on or before the application deadline.</p>
Other	*Deadlines are at 5:00 p.m. (ET). If deadlines fall on a weekend or a federal holiday, the deadline will be the following Monday or the next day after the federal holiday.



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I. Introduction

Summary of Program

The Patient-Centered Outcomes Research Institute (PCORI) is launching this funding initiative to support patient-centered comparative clinical effectiveness research (CER) that addresses important questions about the diagnosis, treatment, and management of hepatitis C. Through this PCORI funding announcement, PCORI seeks to fund pragmatic clinical trials (PCTs), or comparative observational studies with sufficient sample size to address the research question and that will generate information that is readily generalizable to the broader population.

Competitive applications must address at least one of the four priority research questions described in this funding announcement. Additionally, applications should:

- Include patient populations representative of the underlying epidemiology of hepatitis C infection.
- Have strong endorsement and participation by relevant stakeholders, including patient organizations, professional organizations, manufacturers, and/or payer or purchaser organizations.
- Take place within typical clinical care and community settings.
- Have a sufficiently large study population to enable precise estimates of effect sizes and to support evaluation of potential differences in intervention effectiveness in patient subgroups such as racial/ethnic minority populations and individuals with low socioeconomic status.
- Describe, to the extent possible, what can be learned about the natural history of disease and treatment heterogeneity.
- Compare the effectiveness¹ of two or more alternatives for improving patient-centered outcomes.

Background

Hepatitis C virus (HCV) causes a potentially lethal infection that can damage the liver, causing cirrhosis or liver cancer. This condition imposes significant burdens for patients, their families, and the US healthcare system due to its high prevalence, long-term unpredictable disease progression, low rates of detection and treatment, and challenging treatment adherence concerns. It is the most common blood-borne infection, with chronic hepatitis C affecting approximately 2.7–3.9 million Americans and as many as 150 million people worldwide.² Additionally, it is the leading indication for liver transplantation in

¹ Effectiveness is the extent to which an intervention does more good than harm in a broad mix of patients when provided under the usual circumstances of healthcare practice (modified from ec.europa.eu/enterprise/sectors/healthcare/files/docs/rea_principles_en.pdf).

² Centers for Disease Control and Prevention. (2011). Viral hepatitis C surveillance, United States, 2011. Atlanta, GA: Centers for Disease Control and Prevention.

<http://www.cdc.gov/HepatitisC/Statistics/2011Surveillance/index.htm>

the United States.³ The direct and indirect costs attributable to this infection were about \$6.5 billion in 2013.⁴

HCV infection is concentrated, though not exclusively so, in socially and economically disadvantaged groups (e.g., IV drug users, HIV patients, people with serious mental illness, and prisoners). The risk of HCV infection is also higher among blacks and Hispanics, people with lower levels of education, and individuals living below the poverty line.⁵ Among different racial groups, compared with non-Hispanic whites, non-Hispanic blacks have nearly twice the odds, and Mexican Americans have more than two and a half times the odds, of contracting HCV.⁶ People with a family income below the poverty line have a substantially higher probability of testing positive for HCV antibodies.⁷ In addition, persons born between 1945 and 1965 have an increased prevalence of HCV, and a one-time screening of all persons in this birth cohort has been recommended by the US Preventive Services Task Force.⁸ The majority of Americans with HCV infection remain undiagnosed and thus untreated.⁹

Recently, substantial developments have occurred in the availability of new treatment options for this condition. Beginning in the early 2000s, standard therapy for HCV was a combination regimen of pegylated interferon and ribavirin.¹⁰ Although these treatments are effective for some individuals with HCV, only about 50 percent of patients achieve sustained virologic response (SVR)¹¹ and many individuals experience significant side effects.¹² Clinical research also established that patient response rates vary by the genotype of the virus, with genotype 1 being both the most common strain and in some ways the most difficult to treat in the United States. In 2011, the Food and Drug Administration (FDA) approved two directly acting antiviral (DAA) protease inhibitors, telaprevir and boceprevir, for use in combination with pegylated interferon and ribavirin.¹³ Although these DAA therapies improve SVR

³ Razavi H, Elkhoury AC, Elbasha E, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. *Hepatology*. 2013; 57(6):2164–70.

⁴ *Ibid.* p. 2167

⁵ Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *New Engl J Med* 1999; 341: 556-62.

⁶ Institute of Medicine (IOM). (2010). *Hepatitis C and liver cancer: a national strategy for prevention and control of hepatitis B and C*. Washington, DC: The National Academies Press, 1–232.

⁷ Clark P, Muir A, *Overcoming Barriers to Care for Hepatitis C – Perspective*. *N Engl J Med* June 28 2012

⁸ Moyer VA, on behalf of the US Preventive Services Task Force. Screening for hepatitis C virus infection in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2013; 159:349–57.

⁹ Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HEPATITIS C) infection and hepatitis C-related chronic disease. *MMWR Morb Mortal Weekly Rep*. 1998; 47:1–39.

¹⁰ Chou R, Bougatsos C, Blazina I, Dana T, Cantor A. (January 2013). Treatment of hepatitis C virus infection in adults: future research needs. Future Research Needs Paper No. 28. (Prepared by the Oregon Evidence-Based Practice Center under Contract No. 290-2007-10057-I.) AHRQ Publication No. 13-EHC021-EF. Rockville, MD: Agency for Healthcare Research and Quality. Addendum added April 2013.

www.effectivehealthcare.ahrq.gov/reports/final.cfm.

¹¹ US Food and Drug Administration. (2013). FDA approves new treatment for hepatitis C virus [Press Release]. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm418365.htm>.

¹² Institute for Clinical and Economic Review (2014). The comparative clinical effectiveness and value of novel combination therapies for the treatment of patients with genotype 1 chronic hepatitis C infection [Executive Summary]. California Technology Assessment Forum, ES1-ES9.

¹³ Hickam D, Whicher D, Szydowski V. (October 2014). Summary of recently published studies on treatments for

rates, they are associated with significant side effects. In 2013, the FDA approved two additional DAAs, sofosbuvir and simeprevir, for use in combination with pegylated interferon and ribavirin for treating genotype 1 infection. These newer agents are effective with a shorter treatment duration, and evidence suggests they are better tolerated than traditional longer-duration treatment regimens required for pegylated interferon and ribavirin^{14,15}. In 2014, the FDA approved two interferon-free treatment regimens for the treatment of HCV genotype 1. One regimen consists of a single combination pill of sofosbuvir and ledipasvir.¹⁶ The other regimen includes the combination of ombitasvir, paritaprevir, dasabuvir, and ritonavir.¹⁷ These new combinations appear to achieve SVR rates of 80–90 percent. Other new DAAs are also currently in development. These new combination therapies cost approximately \$65,000 to \$190,000 per course of therapy depending on treatment duration.¹⁸

Although the recent approval of new medications offers the promise of transforming HCV treatment, the trials that established their efficacy had short-term SVR as the principal outcome, and only limited post-marketing data are available to date. Data are particularly needed on longer-term effectiveness of the new therapies, on the comparative effectiveness of these therapies, and on a set of treatment outcomes relevant to patients, including symptoms of the infection, drug side effects, treatment adherence, and quality of life. Information about treatment population differences in effectiveness and other issues related to patient preferences is also needed. In addition, questions remain about optimal methods for screening large and difficult-to-reach populations, and on the most effective approaches to deliver treatment and sustain treatment effectiveness, particularly in higher-risk populations.

Research Topic Prioritization

PCORI relies on input from multiple stakeholders to set its research priorities. Members of its advisory panels include patients, clinicians, researchers, purchasers, payers, industry, and other healthcare stakeholders. Many stakeholders have asked PCORI to consider funding research on HCV treatment, which PCORI's Advisory Panel on Assessment of Prevention, Diagnosis, and Treatment Options then ranked as a high-priority topic when it met on September 12, 2014. PCORI then convened a large multi-stakeholder workshop on October 17, 2014, to provide further input on whether specific HCV-related CER questions could be addressed by PCORI-funded research. More than 40 invited stakeholders attended in person. The meeting was open to the public via teleconference and webinar.

Before the workshop, PCORI asked invited participants to propose specific CER questions about HCV. PCORI staff grouped the questions into four categories: care delivery, screening and diagnostic tests,

hepatitis C working document. (Prepared for a PCORI Patient Stakeholder Workshop.) Washington, DC: Patient-Centered Outcomes Research Institute.

¹⁴ Afdhal N, Zeuzem S, Kwo P, et al. ION-1 investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med*. 2014;370(20):1889–98.

¹⁵ Afdhal N, Reddy KR, Nelson DR, et al. ION-2 investigators. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med*. 2014;370(16):1483–93.

¹⁶ US Food and Drug Administration. (2014). FDA approves first combination pill to treat hepatitis C [Press Release]. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm418365.htm>.

¹⁷ US Food and Drug Administration. (2014). FDA approves Viekira Pak to treat hepatitis C [Press Release]. <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm427530.htm>.

¹⁸ Kim WR. The burden of hepatitis C in the United States. *Hepatology*. 2002;36(5 Suppl 1):S30–34.

head-to-head trials of DAA drugs, and timing of treatment in defined patient populations. These questions were discussed, revised, and ranked by the participants during breakout sessions at the workshop.

The workshop concluded with a plenary session during which breakout group leaders presented the ranked questions to all the participants, who were then given five votes that they could distribute among their preferred research questions. PCORI staff used the results of this ranking to inform its selection of four high-priority research questions. These questions were reviewed and approved by PCORI's Board of Governors as the basis for this targeted funding announcement.

Priority Research Questions

Applications should propose PCTs or comparative observational studies that address one or more of the following four priority research questions. The critical difference between the two designs is that the intervention is assigned randomly to a participant in a PCT, while it is dictated by clinical factors in an observational study. Pragmatic trials are designed to maximize applicability of the study's results in routine clinical practice. They tend to be conducted in routine clinical care settings, and in many cases, they must be relatively large, in part to be able to demonstrate differences in comparative effectiveness between different patient subgroups. They should impose fewer constraints on usual practice than traditional randomized control trials (RCTs). The protocols for these trials are typically less complex than efficacy studies^{19,20}.

Observational studies are appropriate when randomization is not feasible, and when rich, population-based clinical data can be obtained in whole or in part from existing databases. Estimates of differences in effectiveness between two active interventions or therapies (i.e., comparative effectiveness) may be relatively small, but nevertheless important—if real. The threat that selection bias or confounding may explain modest differences in observational studies is great. Therefore, applicants proposing observational studies should carefully explain how such bias will be minimized and evaluated.

The four priority research questions are:

- How do new regimens of oral antiviral medications for the treatment of hepatitis C infection compare in long-term virologic response and adverse effects?
- What are the comparative benefits and harms of treating patients with hepatitis C infection at the time of diagnosis versus waiting to treat only those patients who show early signs of progression of liver disease or other manifestations of hepatitis C infection?
 - What are the predictive factors of liver disease progression? How can they be combined to predict patients at low risk of progression?
- Which HCV screening methods, confirmatory testing strategies, and clinical settings lead to the

¹⁹ Patsopoulos, NA. A pragmatic view on pragmatic trials. *Dialogues Clin Neurosci*. 2011; 13:217–24. <http://ncbi.nlm.nih.gov/pmc/articles/PMC3181997/>.

²⁰ Thorpe, KE, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *CMAJ*. 2009; 180:E47–57. <http://cmaj.ca/content/180/10/E47.full.pdf>.

best rates of detection and linkage to treatment?

- What is the comparative effectiveness of interventions to support the care of hard-to-treat patients with chronic hepatitis C infection (e.g., substance abusers, persons with complex medical regimens, the mentally ill), as measured by receipt of treatment, medication adherence, patient quality of life, and sustained viral response?

Additional information related to each of these four priority research questions is provided below.

How do new regimens of oral antiviral medications for the treatment of hepatitis C infection compare in long-term virologic response and adverse effects?

Despite the promising potential benefits of new interferon-free treatment regimens, there is a lack of sufficient information about the long-term results of treatment, especially as treatment moves to routine clinical settings and populations. While studies of interferon and ribavirin have found that SVR appears to be a good predictor of the subsequent clinical course, those studies were based on drug regimens lasting many months. The published studies of the newer drug combinations have largely been based on SVR measured at 12 weeks and have not included long-term follow-up. It is not known whether the experience with the newer shorter regimens will show the same correlation of SVR and clinical outcomes over long-term follow-up as was observed with prior interferon-based regimens. It also is likely that SVR rates when the drugs are used in real-world settings will be modestly lower than was reported in the clinical trials conducted in controlled clinical settings. There is an important knowledge gap about viral response rates (and other clinical outcomes) in populations that have important comorbidities, socioeconomic disadvantages, and other barriers to clinical care.

Balancing the potential benefits and harms of new drug combinations is an important consideration for patients and their clinicians. If regimens differ in side effect profiles or the complexity of dosing schedules, adherence to those regimens may differ. The new medications also are very expensive, with costs for the drugs (based on average wholesale prices) reaching nearly \$100,000 for a single treatment course. Decision makers must have accurate information on which to base the high-stakes decision of choosing an antiviral drug regimen. No head-to-head comparisons have been conducted to evaluate longer-term outcomes of using different FDA-approved DAA regimens.

PCORI is interested in receiving applications that propose to conduct direct comparisons of alternative antiviral treatment regimens. Applicants should provide a convincing explanation for the relevance of treatment regimens compared in the proposed study, citing evidence gaps that are justified on the basis of up-to-date literature reviews. The proposed studies should compare regimens with distinctly different drug combinations. PCORI is particularly interested in studies in populations with important disparities, important comorbidities, or difficult social conditions. PCORI is not interested in research studies designed to compare different durations of the same treatment regimen.

Applicants must consider the broad range of outcomes that are important to patients. In addition to measures of SVR, proposed studies must include measures of drug side effects and systemic symptoms that may be due to HCV viremia, progression of liver disease (both short and long term), and signs of recurrent HCV infection. PCORI is particularly interested in understanding long-term viral response. Therefore, applicants should consider a minimum 2-year follow-up for viral response outcomes and

should obtain patients' permission for passive follow-up through insurance claims data sets and other means. Adaptive study designs that could accommodate the appearance of new treatments during the course of the study are also of high interest. When necessary, blinding and other methods should be used to protect from bias in the ascertainment of outcomes.

What are the comparative benefits and harms of treating patients with hepatitis C infection at the time of diagnosis versus waiting to treat only those patients who show early signs of progression of liver disease or other manifestations of hepatitis C infection?

What are the predictive factors of liver disease progression? How can they be combined to predict patients at low risk of progression?

Chronic HCV infection can cause advanced cirrhosis of the liver, hepatocellular carcinoma, liver transplantation, and death, but disease progression is relatively slow. A systematic review of 111 mostly cross-sectional studies in clinical settings using biopsy to detect liver disease showed that 16 percent of patients with chronic infection had cirrhosis at 20 years following diagnosis of HCV infection, and 41 percent had cirrhosis at 30 years²¹. The progression is faster for individuals with the following characteristics: older age at initial infection, male gender, and excessive alcohol intake. The average annual probability of transition from one stage (F0 [no fibrosis], F1, F2, F3, F4) to another was 10 percent²². This meta-analysis was important for describing the pace of hepatic fibrosis in patients who had clinical evidence of liver disease. It shows that, while the majority of HCV patients do not suffer serious long-term effects, and many experience slow progression of liver fibrosis, the burden of HCV-related illness can be substantial over 20 years or more.

Whether treatment at various stages of liver fibrosis is equally protective against progression to advanced liver disease is not known with certainty. In long-term studies of patients who had HCV-related advanced fibrosis or cirrhosis,²³ achieving an SVR after treatment (with interferon and ribavirin) was associated with an 8.9 percent all-cause mortality rate (versus 26.0 percent in patients who did not achieve an SVR). Treatment that achieved an SVR was associated with a lower 10-year cumulative incidence of liver-related death or transplantation (1.9 percent versus 27.4 percent), liver cancer (5.1 percent versus 21.8 percent), and liver failure (2.1 percent versus 29.9 percent).²⁴ This evidence implies that treatment in the earlier stages of fibrosis can also prevent advanced liver disease, but it does not address the effect of delaying treatment after diagnosis but starting it in the early stages of liver fibrosis, since the patients all had advanced fibrosis when treated. According to the predictions of a recent modeling study, delaying treatment for a few years in the early stages of HCV infection may not be

²¹ Thein, H.-H., Yi, Q., Dore, G. J. and Krahn, M. D. (2008), Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: A meta-analysis and meta-regression. *Hepatology*, 48: 418–431. doi: 10.1002/hep.22375

²² Ibid

²³ Van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA*. 2012; 308:2584–93.

²⁴ Veldt BJ, Healthcote J, Wedemeyer H, Reichen H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. *Ann Intern Med*. 2007; 147:677–84.

harmful,²⁵ but direct evidence is lacking (and may never become available if early treatment becomes the norm).

If only a fraction of chronic HCV patients suffer long-term effects of infection, it is possible that the harms of immediate treatment (as well as the cost of insurance co-payments) could outweigh the benefits for some patients. All patients face costs and harms. Some patients benefit by avoiding symptoms of infection, while others might benefit by avoiding long-term sequelae. The most direct test of early versus delayed treatment would be a randomized trial comparing treatment at the time of diagnosis with treatment at some later date and using patient-reported outcomes (PROs) (with blinding to treatment status) to assess the effect of early treatment on nonspecific symptoms of infection that might cause disability. Such a study could also measure longer-term outcomes of delayed treatment, especially if claims data and death indexes were used to assess long-term outcomes. However, such a trial, in which some patients are randomized to delayed treatment, may not be feasible. Given the apparently high rates of SVR with newer therapies, many patients may no longer perceive equipoise in the question of early versus delayed therapy. If costs of therapy and co-payments decline, as many predict, recruitment would prove even more difficult.

A long-term observational study could use natural experiments to assess the effects of delayed versus immediate treatment on long-term outcomes. In an observational study, a cohort of patients treated at various times after diagnosis of HCV infection would be followed through insurance claims and electronic medical record (EMR) data (self-reported outcomes), the national death index, and/or other data sources, to measure the impact of delayed treatment on development of liver cirrhosis and its sequelae, and on a range of other patient-relevant outcomes. PCORI is particularly interested in long-term response to antivirals, so applicants should consider designs that allow them to assess SVR for a minimum of 2 years. Differing policies about insurance coverage for HCV treatment would afford one form of a natural experiment. Applicants for funding to perform such a study would have to demonstrate variability in access to HCV treatment in defined cohorts; the prospects that such variation would be great enough and last long enough to detect smaller, but meaningful differences in outcomes; and a clear plan for accounting for residual self-selection effects (confounding). An observational study might complement a randomized trial, since it would be more likely to achieve sufficient patients to detect small differences in outcomes following delayed treatment.

Which HCV screening methods, confirmatory testing strategies, and clinical settings lead to the best rates of detection and linkage to treatment?

Current guidelines on the control of HCV infection are based on indirect evidence that detection of infection prior to signs of liver disease will reduce serious long-term outcomes. The guidelines recommend screening for defined population groups, including the 1945–65 birth cohort, IV drug users and incarcerated populations. Many people from these populations typically have little contact with the medical care system, and, in a Center for Disease Control (CDC) demonstration project, only 46 percent

²⁵ Kabiri M, Jazwinski AB, Roberts MS, Schaefer AJ, et al. The changing burden of hepatitis C virus infection in the United States: model-based predictions. *Ann Intern Med.* 2014; 161:170–80.

returned for diagnostic testing after a positive HCV antibody test.²⁶ Conventional HCV testing detects HCV antibody, which proves exposure, but it does not detect the viral genome or core antigen, whose presence proves active infection and justifies starting treatment. Especially for these high-risk patients, being told that active infection is present may motivate them to return for disease staging and treatment (in the CDC study, only 24 percent of those referred for care of active HCV infection kept the first follow-up appointment). Such is the rationale for one-visit care that combines screening and diagnostic testing, a strategy that has not been compared with conventional testing.

The evidence base for screening is relatively narrow. No study has compared clinical outcomes between screened patients and not-screened patients, so that the recommendation for screening rests on a chain of evidence. According to a 2013 systematic review for the US Preventive Services Task Force, four studies have used different combinations of hepatitis C risk factors to predict the screening test results.²⁷ These studies show that increasing the number of risk factors that must all be present to define a high-risk individual will lower sensitivity but increase specificity of the prediction model. These studies did not measure clinical outcomes or the effects of screening on subsequent HCV transmission risk. HCV antibody testing is highly accurate in detecting active infection as compared with the gold standard of polymerase chain reaction (PCR) (sensitivity 97–100 percent) but is also usually positive in patients who have cleared the initial infection. HCV tests include qualitative and quantitative PCR tests, which detect the viral genome. Data from Europe suggest that the HCV core antigen assay can be used as an alternative to PCR for diagnosing current HCV infection and is available on a same-day basis, but the core antigen test is not available commercially in the United States. Same-day PCR is not currently available.

PCORI encourages applications that propose to compare strategies for linking HCV screening to HCV diagnosis, appropriate follow-up care, and ultimately, treatment. Proposed studies should target populations at high risk of active infection, as defined by the CDC but expanded to include both pregnant women and hard-to-reach individuals (including, but not limited to, the incarcerated, the homeless, and those without a primary care clinician).

Among the variables to consider are:

- The HCV screening test (detects antibody versus detects viral proteins or genome)
- How soon the HCV screening test results become available (the day of the blood draw versus later)
- How soon the results of the test to establish active infection become available (the day of the blood draw versus later)
- The diagnostic test to establish active infection (i.e., PCR, core antigen, or other)
- Protocols or other measures for ensuring patient contact and coordinating follow-up care

²⁶ Ward M, personal communication, January 15, 2015

²⁷ Chou R, Cottrell EB, Wasson N, Rahman B, Guise J-M. Screening for hepatitis C virus infection in adults: A systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2013; 158:101-108.

Applicants should justify the choice of screening strategies included in the proposed study and, if proposing the use of tests that are not commercially available in the United States, ensure that the test will be made available for the study. Outcomes should include measures of adherence to follow-up visits, starting treatment (if it is available to the patient), and measures of treatment outcome. While PCORI encourages applicants to consider a broad range of outcomes that are important to patients, attendance at an ongoing source of care for hepatitis C is an essential outcome measure.

What is the comparative effectiveness of interventions to support the care of hard-to-treat patients with chronic hepatitis C infection (e.g., substance abusers, persons with complex medical regimens, the mentally ill), as measured by receipt of treatment, medication adherence, patient quality of life, and sustained viral response?

A substantial proportion of the US population infected with HCV have serious mental illness or are intravenous drug users. Data collected by a multisite study funded by the National Institute of Mental Health suggest that 19.6 percent of adults with severe mental illness are infected with HCV.²⁸ Injection drug use is the strongest risk factor for HCV infection.²⁹ An estimated 60 percent of current HCV transmission in the United States is attributed to injection drug use.³⁰

Due to concerns about nonadherence and potential risk for reinfection, substance abuse and mental illnesses have been important barriers to treatment for HCV.³¹ Part of the difficulty with treating such high-risk populations is that they are often lost to the healthcare system at many different stages, from screening to disease confirmation to care and treatment.³² Optimal models for providing support to high-risk patients during treatment have not been well defined. Some organizations have tested models that integrate HCV treatment with behavioral and social support to promote medication adherence and healthy behaviors designed to reduce the risk for reinfection. To date, there is a lack of rigorous evidence about what systems-level interventions work best in whom, and whether treatment adherence support beyond simple educational materials is beneficial for HCV-infected patients who are prescribed the newer drug regimens. There also is insufficient evidence about how to integrate treatment modules for drug abuse with antiviral treatment programs to keep intravenous drug users free of infection over the long term.

²⁸ Rosenberg SD, Goodman LA, Osher FC, et al. Prevalence of HIV, hepatitis B, and hepatitis C in people with severe mental illness. *American Journal of Public Health*. 2001; 91:31–7. [CrossRef] [Medline].

²⁹ Williams IT, Bell BP, Kuhnert W, Alter MJ. Incidence and transmission patterns of acute hepatitis C in the United States, 1982-2006. *Arch Intern Med*. 2011 Feb 14; 171(3):242-8.

²⁹ Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med*. 2006; 144:705–14. doi:10.7326/0003-4819-144-10.

³⁰ Williams IT, Bell BP, Kuhnert W, Alter MJ. Incidence and transmission patterns of acute hepatitis C in the United States, 1982-2006.

³¹ Groessl, EJ, et al. (2013). Increasing antiviral treatment through integrated hepatitis C care: a randomized multicenter trial. *Contemporary Clinical Trials*. 2013; 35(2):97–107.

[http://www.contemporaryclinicaltrials.com/article/S1551-7144\(13\)00069-4/pdf](http://www.contemporaryclinicaltrials.com/article/S1551-7144(13)00069-4/pdf)

³² Viner K, Kuncio D, Newbern EC, Johnson CC. The continuum of hepatitis C testing and care. *Hepatology*. 2014. doi: 10.1002/hep.27584.

PCORI is interested in studies that compare alternative models for providing support of care for HCV populations deemed hard to treat due to their risk for nonadherence and reinfection. We encourage support models that help coordinate health services throughout the continuum of care, from screening and diagnosis to follow-up, to ensure sustained behavioral changes. The populations can include those with a history of concomitant substance abuse, those with unmanaged depression or severe mental illness, patients lacking adequate social support, or those taking complex drug regimens (such as patients coinfecting with HIV). Outcomes should include measures of viral eradication, adherence to antiviral regimens, changes in clinical measures of comorbidities, and avoidance of reinfection over 1 year.

PCORI encourages programs that address both medication adherence and prevention of reinfection and that integrate hepatitis C treatment with mental and behavioral health interventions. Examples of care models that may be appropriate for such studies include:

1. Multidisciplinary specialized care, such as specialized hospital based clinics, drug detoxification programs, and community-based clinics³³. Multidisciplinary teams generally include clinicians and nursing staff for clinical assessment and monitoring, drug and alcohol support services, psychiatric services, social work, and other social support services (including peer support, if available)³⁴. Proposed comparisons should focus on identifying the minimum essential set of services that can promote positive outcomes.
2. Integrated care: A variety of hepatitis C care models for patients with substance abuse problems have been described—including integrating Hepatitis C care into both primary addiction care and into primary care settings³⁵.
3. Peer-based models of treatment: Both peer- and provider-led group treatment models are familiar, well received, and efficient in the substance abuse treatment setting. Similar to the self-help system, the peer group offers support and influences members to adopt healthy behaviors³⁶.

PCORI is not interested in proposals to study the efficacy of a new model of care, nor of comparisons of

³³ Bruggmann P, Litwin, A. Models of care for the management of hepatitis C virus among people who inject drugs: one size does not fit all. *Clinical Infectious Diseases*. 2013; S56–51.

³⁴ Grebely J, Knight E, Genoway KA, et al. Optimizing assessment and treatment for hepatitis C virus infection in illicit drug users: a novel model incorporating multidisciplinary care and peer support. *Eur J Gastroenterol Hepatol* 2010;22:270–7. Curcio F, Di MF, Capraro C, et al. Together . . . to take care: multidisciplinary management of hepatitis C virus treatment in randomly selected drug users with chronic hepatitis. *J Addict Med* 2010; 4:223–32. Jack K, Willott S, Manners J, Varnam MA, Thomson BJ. Clinical trial: a primary-care-based model for the delivery of anti-viral treatment to injecting drug users infected with hepatitis C. *Aliment Pharmacol Ther*. 2009; 29:38–45. Hill WD, Butt G, Alvarez M, Krajden M. Capacity enhancement of hepatitis C virus treatment through integrated, community-based care. *Can J Gastroenterol*. 2008; 22:27–32.

³⁵ Bruggmann P, Litwin, A. Models of care for the management of hepatitis C virus among people who inject drugs: one size does not fit all. *Clinical Infectious Diseases*. 2013;S56–51

³⁶ Bruggmann P, Litwin, A. Models of care for the management of hepatitis C virus among people who inject drugs: one size does not fit all. *Clinical Infectious Diseases*. 2013; S56–51.

a model of care to “usual care.” Comparators must be, at a minimum, clearly described programs equivalent to “optimal medical management.” That is, the study must be a head-to-head comparison of two active interventions. Studies should measure the content of care that individual patients receive.

Funds Available

PCORI has devoted up to \$50 million in total costs under this PCORI Funding Announcement (PFA) to fund high-impact studies related to the diagnosis, treatment, and management of HCV. The proposed budget for individual studies may range up to \$20 million in total direct costs as appropriate, depending on the specific priority research question or questions the study proposes to address. The maximum project period is 5 years.

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

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

It is expected that project budgets and duration will vary substantially, depending on the topic and approach selected, needs for recruitment and/or primary data collection, length of follow-up, and analytic complexity. PCORI seeks efficient studies, such as those that take advantage of large populations already under observation, registries, and the supportive involvement of delivery systems or health plans to enhance recruitment, data collection, and coverage of treatment-related costs. A prolonged recruitment period is not an acceptable rationale for longer studies. Funding requests to develop or build on initial collaboration between researchers and patient/stakeholder groups are also not appropriate for this funding announcement.

II. Guidance for Preparing Applications

Specific Requirements

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

- Focus on a comparative effectiveness question that is important to patients and other decision makers.

- Address a research gap that has been either substantiated by an existing (recent or updated) rigorously conducted systematic review or specifically emphasized by an official professional society's clinical practice guideline.
- Receive endorsement by relevant patient organizations, clinician organizations, payer/purchaser consortia, and/or life sciences industry representatives as potentially answering a critical question, one that if adequately answered would substantially improve decision making.
- Propose a sample size that is sufficiently large to allow for precise estimation of hypothesized effect sizes or for clear demonstration of noninferiority; in addition, the sample size must support testing of a priori hypotheses related to potential differences in effectiveness in relevant patient subgroups (heterogeneity of treatment effects [HTE]).
- Examine diverse populations receiving care in real-world settings.
- Have strong interest from and support by host delivery systems and clinical care settings.
- Specify broad and simple eligibility criteria that will allow wide generalization of results, while attending appropriately to any ethical concerns of excess risk in some patient subgroups.
- Compare interventions that are known to be efficacious, effective, or commonly in use, and can be implemented in real-world settings.
- Include PROs as a primary outcome, when appropriate.
- Provide preliminary evidence of the potential for efficient recruitment, high participation rates, and appropriate oversight by local or centralized Institutional Review Boards (IRBs), including plans for streamlining or waiving individual informed consent in cases of low-risk interventions. PCORI believes that the intensity of oversight and the complexity of informed consent procedures should be closely related to the degree of risk from study participation. Applicants must address this issue and should present evidence that the study will not encounter significant barriers to recruitment or participation.
- Adhere to all applicable [PCORI Methodology Standards](#).³⁷
- In the case of randomized trials, also adhere to current best practices (standardized inclusion and exclusion criteria; proper randomization; techniques to minimize potential for missing data; appropriate safety monitoring, including establishment of a data and safety monitoring board [DSMB] or indication of why such a board is unnecessary).
- Indicate willingness and include a proposed plan for sharing de-identified data for access by other researchers following completion of the study.

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

³⁷ Available at pcori.org/research-we-support/research-methodology-standards/.

- Identify and engage with major patient and stakeholder organizations that would implement study findings—as well as with existing local communities of patients and care providers—to formulate the research questions, design the study, help monitor progress, and disseminate the findings.
- Minimize disruption to participants' daily routines (e.g., minimize participant visits intended solely for study-assessment purposes; capture PROs during office visits, electronically or via phone).
- Design the study so that the conduct can, as seamlessly as possible, be integrated with routine clinic or office operations.
- Use efficient methods to obtain participant consent while still meeting ethical and legal requirements.
- Capitalize on the existing electronic health records and other computerized information to identify and recruit eligible patients, monitor study conduct and patient safety, and collect study outcomes information.
- If data standardization and interoperability across study sites has not already been accomplished, develop methods that will enhance the standardization of data that are accessed from different electronic health record systems.

Nonresponsiveness

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

- Tests efficacy (or comparative efficacy) within a tightly protocol-controlled research setting (as opposed to more real-world, pragmatic CER)
- Conducts a cost-effectiveness analysis in the form of dollar-cost per quality-adjusted life-year to compare two or more alternatives
- Directly compares the costs of care between two or more alternative approaches
- Measures the relative costs of care of two or more alternative approaches as the primary criteria for choosing the preferred alternative
- Conducts studies of the natural history of disease, instrument development, pharmacodynamics, and fundamental science or study of biological mechanisms
- Evaluates new or existing decision support tools; this includes the development and evaluation of a decision support or shared decision tool or system for patients, clinicians, or both patients and clinicians
- Develops clinical prediction or prognostication tools

Proposals that include studies of these issues may measure and report use of any or all health services, but may not employ direct measurements of care costs.

PCORI does have an interest, however, in studying conditions that lead to high costs to the individual or to society. Thus, PCORI is also interested in studies that:

- Address cost-related issues, such as the resources needed to replicate or disseminate a successful intervention.
- Evaluate interventions to reduce health system waste or increase health system efficiency.

Proposals that include studies of these issues without using cost-effectiveness analyses or comparing the costs of alternatives are considered responsive.

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

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

Features of Patient-Centered Outcomes Research (PCOR)

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

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

Leveraging Existing Resources

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

Preliminary Data and Use of Accepted Measures

PCORI encourages investigators to design their research using valid patient-centered outcomes measures and include preliminary data that supports the proposed measures. Investigators are encouraged to consider those measures described in the *Patient Reported Outcomes Measurement Information System (PROMIS)*.³⁸

Documentation of Assumptions

PCORI specifically seeks studies that are sufficiently powered to detect clinically meaningful effects. To

³⁸ Available at <http://nihpromis.org/>.

that end, applicants must justify the proposed sample sizes by explaining the assumptions used in all study power calculations. The application should clearly state all the necessary assumptions (i.e., the primary outcome measure, the estimated difference in the mean value of this measure between study arms, standard deviation of the measure, type I error rate, and any other assumptions). All such estimates must be justified by referring to prior published research or preliminary data.

Methodological Considerations

Regardless of study design, proposals must adhere to all relevant [PCORI Methodology Standards](#).³⁹ These include 47 individual standards that fall into 11 categories. The first five categories are cross-cutting and are relevant to most PCOR studies. Researchers should refer to all of these standards when planning and conducting their research projects. These five categories are:

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

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

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

Most of these standards should be considered “minimal” standards. Additional best practices, including relevant guidelines for the conduct of clinical trials developed by other organizations, should be addressed in the application for PCORI funding. To help reviewers quickly identify the adherence to a particular standard, applicants must cite to each methodology standard within their proposals as the standard is being addressed. For example, when applicants describe the need for their proposed study within the Background section, they should indicate the particular standard for Identify Gaps in Evidence in parentheses, such as “(RQ-1).”

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

³⁹ Available at pcori.org/research-we-support/the-pcori-methodology-report/.

Patient and Stakeholder Engagement

PCORI encourages all applicants to clearly describe the patient and stakeholder engagement in their research proposals. PCORI understands that patient and stakeholder engagement in research can take many forms; it is not seeking one particular type or method of engagement. Rather, applicants should communicate how patients (those with lived experience), family members, caregivers, and the organizations that represent them, as well as any other relevant stakeholders, will be involved in study activities. Because this type of engagement in research is a relatively new concept, PCORI has developed the Engagement Rubric to guide both applicants and merit reviewers. Additionally, studies are expected to adhere to PCORI's Methodology Standards Associated with Patient-Centeredness and to the PCOR Engagement Principles found within the rubric. These and additional resources are available in [PCORI's Funding Center](#).

Populations Studied

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

- Racial and ethnic minority groups
- Low-income groups
- Women
- Children (age 0–17 years)
- Older adults (age 65 years and older)
- Residents of rural areas
- Individuals with special healthcare needs, including individuals with disabilities
- Individuals with multiple chronic diseases
- Individuals with rare diseases
- Individuals whose genetic makeup affects their medical outcomes
- Patients with low health literacy/numeracy and/or limited English proficiency
- Lesbian, gay, bisexual, and transgender (LGBT) persons

Budget and Duration of Project

Applicants may request up to \$20 million in total direct costs for a project period not to exceed 5 years. Note that PCORI will not cover costs for interventions that are being compared in the proposed study (see Appendix 3 in the [Application Guidelines](#) for details). Applicants should submit realistic budgets and timelines. For those rare circumstances in which the estimated total direct costs exceed \$20 million, provide in your Letter of Intent (LOI) a detailed justification that ties the extra expense to the success of the project. Not all requests for additional funds will be approved. Any request for a project period longer than 5 years will be denied. For further information regarding PCORI's policies about allowable and unallowable costs, refer to Appendix 3 of the [Application Guidelines](#).

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

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

Refer to the [Application Guidelines](#)⁴⁰ for a list of additional PFA-specific project milestones.

Collaboration

PCORI is particularly interested in applications that involve community and commercial organizations that can help researchers design, implement, disseminate, and sustain effective interventions. We encourage applications that include novel collaborations with accreditation organizations, credentialing bodies, educational enterprises, patient advocacy groups, industry, professional societies, and subspecialty societies.

Protection of Human Subjects

This component (up to five pages) is included in the Research Plan Template. Describe the protection of human subjects involved in your research. PCORI follows the Federal Policy for the Protection of Human Subjects ([45 CFR part 46](#)), including the Common Rule. For more detailed information, see the Section 5 "Human Subjects Research Policy" from the [Supplemental Grant Application Instructions for All](#)

⁴⁰Available at <http://www.pcori.org/sites/default/files/PCORI-PFA-Hepatitis-C-Application-Guidelines.pdf>.

[Competing Applications and Progress Reports](#),⁴¹ issued by the US Department of Health and Human Services (DHHS). PCORI does not require that applicants comply with sections of this policy that refer to requirements for federal wide assurance (FWA), or that refer to standards for inclusion of women, minorities, and children. PCORI also does not require, but does strongly encourage, applicants proposing clinical trials to consider including a data- and safety-monitoring plan. Awardees must also comply with appropriate state, local, and institutional regulations and guidelines pertaining to the use of human subjects in research.

PCORI merit reviewers will examine plans for protection of human subjects in all applications and may provide comments regarding the plans (see [How to Evaluate Human Subjects Protections](#)⁴²). Reviewers' comments on human subjects research are not reflected in the overall application score, but may be used by PCORI staff during any potential funding negotiations. Final determinations about adequacy of human subject protections rest with the IRB or IRBs that have jurisdiction for the study.

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

[Required Education of Key Personnel on the Protection of Human Subject Participants](#)

PCORI requires all applicants to adhere to the National Institutes of Health (NIH) policy on education in the protection of human subject participants in the conduct of research. This applies to all personnel listed as "key personnel" in the application. The policy and FAQs are available [from the NIH website](#).⁴³

[Replication and Reproducibility of Research and Data-Sharing Plan](#)

PCORI is committed to maximizing the utility and usability of data collected in our funded projects. This is essential to building confidence in the accuracy of these findings. PCORI supports policies to promote sharing of study documentation (e.g., study protocol, programming code, and data definitions) so that other researchers may replicate the findings in other populations. Propose a method for sharing data and appropriate documentation upon request.

[III. How to Submit an Application](#)

[Letter of Intent](#)

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

⁴¹ See <http://grants.nih.gov/grants/funding/424/supplementalinstructions.docx>.

⁴² See <http://www.pcori.org/sites/default/files/PCORI-Checklist-for-Evaluating-Human-Subjects-Protections.pdf>.

⁴³ See <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-054.html>.

Answer all of the questions in the LOI template. This includes the question on brief justification for the proposed cost of the study; providing an answer “the cost not to exceed \$20 million” is not sufficient. Then upload your document to the PCORI Online System. The deadline for LOI submission is March 6, 2015, by 5:00 p.m. (ET).

Letter of Intent Review

LOIs are evaluated on the following criteria:

- Whether the proposed topic addresses one of the high-priority research questions identified in this funding announcement
- Importance of the specific research question (comparison), as evidenced by critical gaps identified by clinical guidelines developers and/or recent relevant systematic reviews
- A sufficient size or scope that the proposed topic will have a significant impact on patient outcomes and/or healthcare practices
- Clarity and credibility of applicants’ responses to the LOI questions, as well as their justification of the proposed size of the study citing published estimates, including effect sizes, standard deviations, and need for rigorous comparative analysis of important subgroups
- Prior relevant experience
- Programmatic fit and balance, taking into consideration whether the research study question and study design are compliant with requirements in this funding announcement
- Adherence to the administrative and formatting requirements listed in the [Application Guidelines](#), specifically the five-page limit for the LOI

LOIs are reviewed qualitatively; they are not scored. Only applicants with LOIs deemed most responsive to this PFA will be invited to submit a full application. Notification of request to submit a full application will be sent on or before March 23, 2015. Refer to the [Application Guidelines](#) for due dates and information on how to submit your LOI in the PCORI Online System.

If your LOI is deemed responsive and you are invited to submit a full application, do not make significant changes to your proposed project without consulting a program officer. For example, you should not revise your major aims or study design. Any significant changes are grounds for removal from the full review process.

Note: An individual may submit only one LOI as a Principal Investigator (PI) for a particular PFA in the same cycle. While a PI may submit an LOI to other PFAs, the research topic/project must be distinct. LOIs with scientific overlap or that appear to be duplicate submissions to different funding announcements within the same cycle will be removed during the LOI screening process.

Submission Dates

LOIs and applications must be submitted in accordance with the published dates and times listed in the overview of this PFA and in the [PCORI Funding Center](#).⁴⁴

⁴⁴ Available at pcori.org/apply.

PCORI Online System

To submit a proposal, you must register with the [PCORI Online System](http://www.pcori.org)⁴⁵ and submit both an LOI and an application for each cycle in which you are applying.

Applicant Resources

PCORI Funding Center <http://www.pcori.org/hepatitis-c-PFA>

PCORI Online System pcori.fluxx.io

PCORI Funding Awards pcori.org/pfaawards

IV. Merit Review

PCORI merit review is a multiphase process that includes:

- Evaluation of LOIs
- Inviting a subset of LOIs to submit full applications
- Administrative and programmatic review of full applications
- Preliminary review by review panels for full applications that meet administrative and programmatic requirements
- In-person review panel discussion of full applications
- Post panel review, an invitation to an in-person or webinar presentation for select meritorious applicants
- In-person or webinar presentation by select applicants
- Post in-person or webinar presentation, Selection Committee deliberation and recommendation of applications for funding
- Board of Governors award approval (no later than September 2015)

Application Review Criteria

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

Criterion 1: Impact and importance of the research aims, interventions, comparators, and outcomes on individuals with hepatitis C and their caregivers, clinicians, employers, insurers, and policy makers

The proposal addresses the following questions:

- Does the research study address an evidence gap that systematic reviews, guideline development efforts, or previous research prioritizations have noted as being of high importance for validating policies for screening, diagnosis, treatment, and/or management of hepatitis C?

⁴⁵ Available at pcori.fluxx.io.

- Does the proposal provide an adequate case that the proposed intervention and comparators will fill the evidence gap?
- Does the application make a convincing case that currently there are wide variations in practice patterns that can be addressed with new evidence?

Criterion 2: Potential for the study results to be incorporated into clinical practice

The proposal addresses the following questions:

- Will the proposed study provide sufficient data about important patient subgroups, so that the data about comparative effectiveness can be applied to particular clinical settings?
- Have the investigators established connections with key organizations responsible for the dissemination or implementation of research results and the development of professional standards of care?
- Have the investigators addressed the implementation and long-term sustainability of successful interventions(s) in the chosen settings?
- Does the application identify facilitators and barriers to implementation, as well as how to surmount the identified barriers?

Criterion 3. Technical merit

The application has sufficient technical merit to ensure that the study goals will be met. It addresses the following questions:

- Is there a clear research plan with rigorous methods that adhere to PCORI’s Methodology Standards and prevailing accepted best practices?
- Is there a clear comparison condition that is a realistic option in standard practice? Is the comparator sufficiently described to reasonably compare the two or more conditions in the trial?
- Are the proposed comparative conditions currently in use? Is there prior evidence of efficacy or effectiveness for the interventions being compared?
- Is there evidence that the outcome measures are sufficiently sensitive to identify differences between groups?
- Is the study conducted in a patient population that is relevant to the majority of patients with a condition or to a previously understudied subgroup?
- Are the prespecified subgroups reasonable given the proposed interventions and condition? Are the subgroups sufficiently large to allow a rigorous and valid comparative analysis?
- Is there a clear and adequate justification for the study design choices in the proposed pragmatic trial?
- Is there an adequate plan for protection of human subjects participating in this study?
- Do the applicants provide evidence of study feasibility based on availability of participants and experienced staff for efficient start-up?
- Does the project include a realistic timeline that includes clear and specific scientific and engagement milestones?
- Does the research team have the necessary expertise and prior experience in conducting large-

scale multicenter trials as well as an appropriate organizational structure to successfully complete the study?

- Is the research environment, including the delivery systems that will host the study, well resourced and highly supportive of the proposed study?

Criterion 4. Patient-centeredness

The proposal demonstrates patient-centeredness at every stage of the research. It addresses the following questions:

- Is the research focused on questions that affect outcomes of interest to patients and their caregivers?
- Does the research address one or more of the key questions mentioned in PCORI's definition of PCOR?

Criterion 5. Patient and stakeholder engagement

The application demonstrates that people representing the population of interest and other relevant stakeholders are engaged in ways that are appropriate and necessary in a given research context.

- Are patients and other stakeholders engaged in:
 - Formulating research questions?
 - Defining essential characteristics of study participants, comparators, and outcomes?
 - Identifying and selecting outcomes that the population of interest notices and cares about (e.g., survival, function, symptoms, health-related quality of life) and that inform decision making relevant to the research topic?
 - Monitoring study conduct and progress?
 - Designing and/or suggesting plans for dissemination and implementation activities?
- Are the roles and the decision-making authority of all research partners clearly stated?
- Does the application demonstrate the principles of reciprocal relationships, co-learning, partnership, trust, transparency, and honesty?

Preliminary Review

PCORI conducts rigorous merit review of the full applications it receives. Applications may be eliminated from the review process for administrative or programmatic reasons (i.e., nonresponsiveness). An application may be eliminated if it is incomplete or submitted past the stated due date and time, or if it does not meet the administrative or formatting criteria outlined in the Application Guidelines, in the PCORI templates, and in the [PCORI Online System](#).⁴⁶ It may also be withdrawn if it is not responsive to the guidelines described in this PFA, describes research that is not comparative, includes cost-effectiveness analysis, or otherwise fails to meet PCORI programmatic requirements. Per our authorizing legislation, if two proposed research plans overlap, funding preference must be given to applications submitted on behalf of NIH and the Agency for Healthcare Research and Quality (AHRQ).

One or more specially convened merit review panels will review responsive applications. PCORI Merit

⁴⁶ Available at pcori.fluxx.io.

Review Officers (MRO) recruit each panel. MROs identify the chair, scientist reviewers who are clinical experts familiar with the clinical content of submitted applications, methodological and statistical experts familiar with PCTs and large database analyses, patient representatives trained in review of scientific proposals, and representatives of other stakeholder groups.

In-Person Review

Once preliminary review is complete, prior to the in-person Merit Review, a team of five members of the Merit Review Panel will review each submitted application deemed administratively and programmatically compliant by using the five criteria and PCORI's Methodology Standards.

During the in-person review, the full panels meet to discuss the applications, further clarify the merits of the proposed research, and identify areas for improvement. Each application is assigned a score based on the content of that discussion. The chair and a PCORI MRO lead the in-person panel meeting and ensure that all applications receive a fair and thorough review informed by the standards outlined in the PFA.

Post-Panel Review

After the in-person panel review, PCORI staff will review the merit review scores and comments, identify duplication or synergy among funded projects, and consider the fit of applications within the programmatic vision. During this process, PCORI staff members may send meritorious applications that remain in consideration to independent methodological experts for their assessment. The goal of this assessment, which is distinct from merit review of the entire application, is to focus specifically on ways to enhance the methodological rigor of proposed study designs.

Program staff then recommend projects to a Selection Committee that includes members of PCORI's Board of Governors and Methodology Committee. 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, PCORI's strategic priorities, and other considerations. This slate is proposed to PCORI's Board of Governors for its consideration and approval.

Board of Governors Approval

The PCORI Board of Governors will consider the selected applications, factoring in the total available funds allotted for this announcement and programmatic needs. PCORI will inform applicants of Board of Governors' decisions no later than September 2015.