1:00 PM  Welcome
Jean Slutsky, PA, MSPH, Chief Engagement and Dissemination Officer; Program Director, Communication and Dissemination Research, PCORI

1:05 PM  Background and goals for the day
PCORI activity to date around hepatitis C
Joe Selby, MD, MPH, Executive Director, PCORI

New business: emerging research question for discussion
Evelyn Whitlock, MD, MPH, Chief Science Officer, PCORI

1:30 PM  Open discussion
Moderator: Joe Selby, MD, MPH

Types of Comments requested:
1) Comments regarding the likely usefulness and relevance of this study when completed – to patients, clinicians, policymakers
2) Comments regarding the scientific merit of the study
3) Comments regarding ethical aspects of the study
4) Other Comments

Order of Comments:
1) Patients and patient representatives
2) PCORI Board of Governors
3) Clinicians
4) Purchasers
5) Industry and researchers
6) Hospitals and health systems
7) Payers and policymakers
8) Patients and patient representatives

2:45 PM  Summary and closing remarks
Joe Selby, MD, MPH

3:00 PM  Workshop adjourns

Agenda

Can CER Help Answer Questions About Hepatitis C? A PCORI Stakeholder Workshop

May 18, 2016
1:00 PM – 3:00 PM

via teleconference and webinar
A proposal for refining the funding announcement for a comparative clinical effectiveness research study of immediate treatment versus active surveillance in people with early stage hepatitis C

Purpose
At the March 2016 Board of Governors meeting, PCORI announced a more focused funding announcement would be released regarding benefits and harms of treating hepatitis C infection at time of diagnosis versus waiting. Shortly afterwards, we heard from concerned patient organizations that further discussion should be held prior to issuance. PCORI agrees and this webinar is intended to re-engage with patients and other stakeholders.

During this webinar we will discuss a newly-proposed research question and study idea. If you would like to comment on this proposal during the webinar, please use the framework on the agenda to organize your comments.

Background
In October 2014, PCORI convened this multi-stakeholder group to consider possible research questions in the detection and treatment of hepatitis C. Four questions came out of the workshop and were included in a PCORI Funding Announcement (PFA):

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

2) 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? Can they be combined to predict patients at low risk of progression?

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

4) 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?

Patients stated at and following the October 2014 workshop that even if no differences in liver disease endpoints were detected, there were also short-term symptoms that can be alleviated with treatment, justifying immediate treatment for all. Patients and clinicians also expressed concerns that sponsoring a 3-4 year randomized trial could serve to delay the spread of coverage for treating early stage disease. Other concerns included a changing landscape in terms of coverage that could make recruitment and retention in a trial more difficult or infeasible, or even raise IRB concerns.

PCORI released a funding announcement in February 2015 and awarded large studies addressing questions #1 and #4 in September 2015. No studies were funded for either question #2 or #3.

This reconvening of our October 2014 workshop is focused on the above question number two related to treatment at time of diagnosis or waiting.
In our Spring 2015 funding announcement, PCORI noted important questions and possible risks and concerns (please see below question number two excerpt from the February 2015 funding announcement, page 5), including:

- [W]hile 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.

- [D]elaying treatment for a few years in the early stages of HCV infection may not be harmful, 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... could outweigh the benefits for some patients.

- All patients face costs and harms.

- 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.
  - However, such a trial, in which some patients are randomized to delayed treatment, may not be feasible. Given the apparently high rates of SVR [sustained virologic response] 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.
  - PCORI is particularly interested in long-term response to antivirals...

PCORI received several funding applications for consideration related to the PFA for question number two. While no study has been funded, PCORI continued to consider the importance of this question and the concerns regarding randomization raised by patients, patient advocates and clinicians. To address concerns, PCORI sought to narrow the focus of question number two to include a potential randomized trial targeted to short-term, patient-centered outcomes only, with longer term outcomes addressed in a complementary observational study. PCORI announced in March a more targeted PFA of two proposed trials:

1. Patient-Centered Outcomes in Optimal Timing for Hepatitis C Treatments
   Among patients with early stage hepatitis C infection (defined as fibrosis stages 0-2) who do not have immediate access to direct-acting antiviral (DAA) treatment, what are the short-term
benefits and harms of DAA treatment on patient-centered outcomes such as quality of life, fatigue, depression, malaise, etc., at treatment end and at 1 year?

Note: PCORI encourages a double-blind randomized controlled trial (of immediate treatment vs. placebo) in clinical settings with policies restricting access to DAA treatment in patients with early stage hepatitis C liver disease with up to 1 year follow up looking at various patient reported outcomes such as patient assessment of disease progression, quality of life, functional status and symptoms, as well as clinical outcomes including SVR.

2. **Long-Term Patient Outcomes in Treatments for Hepatitis C**

What are the long-term outcomes, in terms of liver disease progression and extra-hepatic complications of HCV infection, experienced by patients with early stage (fibrosis stages 0-2) HCV infection, who have not yet received treatment with direct-acting antivirals? PCORI is especially interested in focusing on disproportionately disadvantaged populations who often experience challenges in access to health care services, misuse of alcohol and other substances, and have multiple co-morbid conditions.

It is envisioned that the proposed research should be a prospective cohort study, such as a patient registry with active surveillance and rich clinical practice-based data that incorporates patient-centered outcomes measures.

**Key points regarding the randomized portion of the above refined question 1 (Patient-Centered Outcomes in Optimal Timing for Hepatitis C Treatments)**

- Focused on the potential benefits of immediate treatment on short-term, non-hepatic symptoms in persons with early stage liver disease (fibrosis stages 0-2)
- One-year total duration of treatment and follow-up
- Conducted in low-risk patient populations without current access to immediate DAA treatment
- Double-blind, randomized, placebo-controlled trial (immediate treatment vs. placebo)
  - Patients would be blinded to—would not be informed of—both treatment status and viral load results for 12 months
- Major outcomes are patient-reported symptoms (fatigue, depression, mental cloudiness), quality of life, functional status, patient assessment of disease progression
- Patients in the control treatment (placebo) would receive treatment at the end of the study (after 12 months)
PCORI Funding Announcement Spring 2015 Cycle: Clinical Management of Hepatitis C Infection

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 HVC infection, and 41 percent had cirrhosis at 30 years.\(^2\) 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 percent.\(^2\) 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,\(^2\) 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).\(^2\) 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 harmful,\(^2\) 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.

21 Thein, H.-H., Yi, Q., Dore, G. J. and Krahn, M. D. (2008), Estimation of stage-specific fibrosis progression rates in
22 Ibid
all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012;
308:2584–93.
25 Kabiri M, Jazwinski AB, Roberts MS, Schaefer AJ, et al. The changing burden of hepatitis C virus infection in the