GPC-ICER Web Conference: Hepatitis C Drugs – Evidence to Demonstrate Effectiveness and Value

Summary of Webinar Held July 7, 2014
OVERVIEW
On July 7, 2014, the Green Park Collaborative (GPC) of the Center for Medical Technology Policy (CMTP) and the Institute for Clinical and Economic Review (ICER) co-hosted a web conference to explore the evidence needed to demonstrate the effectiveness and value of new drugs to treat chronic hepatitis C (HCV) infection. Representatives from various stakeholder groups, including payers, patients, pharmaceutical industry, health technology assessment organizations, and regulatory bodies, presented and discussed this issue with a particular focus on:

1. The evidence generated for regulatory approval;
2. The evidence preferences of post-approval decision makers; and
3. Strategies to efficiently generate the additional evidence.

Each of the invited speakers gave a brief presentation followed by a question and answer session at the end of the presentations. Audience members had an opportunity to submit questions through a chat feature. The conference was moderated by Dr. Sean Tunis, Founder and CEO of CMTP. More than 200 participants, including a variety of subject matter experts and stakeholder representatives, attended the web conference.

BACKGROUND
Chronic hepatitis C affects an estimated 3.2 million people in the United States. The disease is associated with serious liver problems and is the nation’s leading cause of liver cancer and liver transplantation. In recent years hepatitis C has surpassed HIV/AIDS as a cause of death. Until recently, the standard of care for chronic hepatitis C has involved up to 48 weeks of therapy that is not suitable for all patients due to serious side effects, risk of drug-drug interactions, and burdensome dosing requirements.

Recently, however, the FDA approved two new medications -- Olysio (simeprevir) and Sovaldi (sofosbuvir) -- that offer the promise of significant clinical advantages. FDA approval was based on clinical trials that demonstrated high rates of viral clearance with relatively low risks of side effects. Sovaldi, in particular, has received notice because it is the first FDA-approved drug to treat patients with certain sub-types of hepatitis C without requiring combination therapy with interferon. However, concerns have been raised about limitations in the evidence currently available for clinical and policy decisions, and what additional evidence would be most helpful for future decision making.

CONFERENCE SUMMARY
SPEAKERS
- Poonam Mishra, MD, Medical Officer, Division of Antiviral Products; FDA
- Gregg Alton, JD, Executive Vice President, Corporate and Medical Affairs; Gilead
- Steven Pearson, MD, MSc, President; Institute for Clinical and Economic Review (ICER)
- Donna Cryer, JD, President and CEO; Global Liver Institute
- Michele Manos, PhD, MPH, DVM, Public Health Consultant
- David Ross, MD, PhD, MBI, Director, HIV, HCV, and Public Health Pathogens Programs, Office of Public Health/Clinical Public Health; VA
- Mark Godwin, PharmD, Manager of Clinical Pharmacy; UnitedHealthcare
The following paragraphs summarize the conference presentations and responses to questions by topic and stakeholder category rather than presenter by presenter.

**CLINICAL TRIAL DESIGN**
Some payers and technology assessors expressed a desire for placebo-controlled randomized clinical trials rather than the single-arm trials with historical controls on which FDA approval was based. The rationale for historical controls was based on: (1) a highly objective outcome measure in sustained virologic response (SVR); (2) consistent success rates across trials; and (3) high treatment SVR rates in the 90%+ range 12 weeks after end of treatment. Given that SVR rates for placebo groups ranged from 40-50%+, however, it was thought that placebo-controlled trials could assist with comparative effectiveness comparisons. Such trials could be ethically acceptable because of the short treatment times in the completed trials although it was recognized that it might be difficult to recruit patients who would be willing to participate.

There was also discussion of active control trials with some indication that regulators may start preferring them to historical controls. Some commenters suggested that from a payer perspective superiority trials would be much preferable to non-inferiority trials as payers would have little incentive to pay more for drugs that have not been demonstrated to be superior to alternatives, i.e., approved through non-inferiority trials.

**“REAL-WORLD” DATA**
Payers, technology assessors, clinicians, regulators, and patient advocates all noted the need for “real world” data, both safety and effectiveness, that potentially could be obtained through large population-based studies in non-academic settings. For example, early data from the VA’s HCV registry indicate that SVR rates in clinical practice are not as high as in the clinical trials. Concerns were expressed by clinicians and technology assessors about the possible development of drug resistance if regimen adherence in the real world is incomplete, and the consequent need for multiple drug therapy. A patient advocate, however, argued that the risk of drug resistance was overstated because the reduced complexity of the newer regimens would be likely to lead to increased compliance. Additional data on real world adherence rates will therefore be useful.

**PATIENT POPULATIONS**
Another common theme, raised by regulators, payers, clinicians, technology assessors, and industry, concerned the need for better information about patient subpopulations. Payers and clinicians indicated a need for information about effectiveness by age (especially for the 50-70 year old group), race and ethnicity, prior treatment history, disease status, co-morbidities (e.g., HIV infection, renal insufficiency), and host and viral genetics, among other factors. Clinicians, payers, and technology assessors raised the related issues of whether there were subgroups of patients who would do well with watchful waiting, at least in the short term, how to best monitor them, and when to start treatment (e.g., based on fibrosis score?). From a patient perspective, however, it was thought that watchful waiting would be generally inappropriate when treatments are available.

**LONG-TERM OUTCOMES**
Virtually all stakeholders emphasized the need for information about the long-term clinical outcomes of patients treated with the new drugs. SVRs achieved through different mechanisms
might well have different clinical outcomes and particular concern was expressed by clinicians about the possible consequences of removing interferon from the treatment regimen. These data could be collected through long-term follow-up and patient registries and some efforts are already underway by industry and government programs to collect these data.

Several other topics were raised by more than one presenter:

- **Comparative Effectiveness.** Although payers, clinicians, technology assessors, and patients were very interested in comparative effectiveness and safety. Patient representatives also noted the need for comparative data on factors such as adherence, absenteeism and presenteeism, quality adjusted life years, and progression of disease. However, stakeholders did not believe there would be many head-to-head trials and therefore the data would likely have to come from observational studies.
- **Duration of Treatment.** Clinicians, industry, and regulators believed it would be helpful to have additional data on the optimal duration of treatment. Would it be possible to stop therapy at eight weeks, for example, if a patient was experiencing significant side effects?
- **Prevention Benefits.** Clinicians and industry raised the question of whether the drugs have any preventive benefits (e.g., decreased transmission, post-exposure prophylaxis)

Other identified needs for research included:

- drug/drug interactions (regulators)
- whether patients with traditional barriers to treatment (e.g., injected drug use, alcohol use) can be treated successfully (clinicians, industry)
- pharmacoeconomic studies designed to demonstrate the true value of treatment regimens, including both pharmacy costs and medical cost savings (payers)
- whether it is possible to define an upper age limit for treatment (clinicians)

**MECHANISMS TO GENERATE EVIDENCE**

Although most of the session focused on identifying research needs, there was some discussion of approaches to facilitate production of the desired evidence. Industry was identified as a potential source of funding for research given their incentive to demonstrate the real world and long term effectiveness and value of their products. Gilead, for example, the sponsor of Sovaldi, is already undertaking a number of studies, including gathering evidence on duration of therapy, historically harder to treat populations, different viral genotypes, pre- and post-transplant patients, patients with HIV co-infections, and patient-related outcomes, among other issues. Other incentives for industry could come from government regulators and payers if they required certain information for product approval or reimbursement.

It was generally recognized that resources were limited and that research funding would have to come from other sources as well. NIH funds are constrained, however, and other HHS have not yet committed significant resources in this domain. Nevertheless, Medicare is going to be increasingly affected by HCV making it a high priority to explore potential sources of federal funding for additional research. Some clinicians pointed to oncology cooperative groups as models for conducting research on population subgroups. Professional societies, and organizations such as the Global Liver Institute were also mentioned as stakeholders who would be interested in becoming involved to answer some of the questions. The collective efforts of
the VA, Kaiser and other integrated delivery systems could also contribute substantially to generating useful real world evidence.

**QUESTIONS FROM AUDIENCE**
Audience members could submit questions through the chat function of the virtual conference. Most audience questions focused on the topics raised by the panel members, such as funding sources, sub populations and the ethics of a placebo controlled studies, while some questions focused on broader questions such as HCV eradication.

**NEXT STEPS**
In closing, Dr. Tunis stated that the slides and full webinar would be posted on the CMTP website and efforts would be made to gather unanswered questions and provide them to the speakers for response. He also informed the participants that GPC would continue collaborating with ICER and other experts and stakeholders to explore potential approaches to addressing some of the high priority areas of uncertainty that were discussed.