WELCOME

HEPATITIS C DRUGS - EVIDENCE TO DEMONSTRATE EFFECTIVENESS & VALUE

July 7th, 2014
The Center for Medical Technology Policy (CMTP) has extensive experience convening stakeholder groups to discuss value, and evidence and methodological standards. CMTP’s work on such standards is conducted under the umbrella of the Green Park Collaborative-USA (GPC-USA), a neutral forum to support dialogue and consensus among stakeholders on methodological standards for clinical research, focusing on “real-world” effectiveness and value, and emphasizing evidence expectations of payers, informed by the views of patients and clinicians. Visit us online at: http://www.cmtpnet.org/

The Institute for Clinical and Economic Review (ICER) is an independent non-profit health care research organization dedicated to improving the interpretation and application of evidence in the health care system. ICER directs two core programs: the California Technology Assessment Forum (CTAF), and the New England Comparative Effectiveness Public Advisory Council (CEPAC). For more information about ICER, please visit ICER’s website, www.icer-review.org.
WEB CONFERENCE CO-HOSTS

CENTER FOR MEDICAL TECHNOLOGY POLICY
GREEN PARK COLLABORATIVE
Sean Tunis, MD, MSc
Founder & Chief Executive Officer

INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW
Steve Pearson, MD, MSc
President

Elisabeth (Els) Houtsmuller, PhD
Vice President and Senior Research Director
New treatment options for hepatitis C appear to have significant advantages in terms of safety, effectiveness, and patient burden.

Evidence needs for decision-making by patients, clinicians, and payers.
HEPATITIS C DRUGS: GPC FOCUS

• GPC Purpose: provide multi-stakeholder forum to support dialogue and consensus on methodological standards for generating evidence of effectiveness and value

• Forward-looking: maximize relevance, quality and efficiency of future research to inform key decision makers (patients, clinicians, and payers)

• Intent of webinar is NOT to debate critical issues of current coverage policies, evidence requirements for breakthrough drugs or accelerated approval, or pricing of medications
### WEB CONFERENCE AGENDA

#### Hepatitis C Drugs - Evidence to Demonstrate Effectiveness & Value

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Speakers</th>
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</thead>
<tbody>
<tr>
<td>Noon</td>
<td><strong>Introduction and Overview</strong></td>
<td>Sean Tunis and Els Houtsmuller, CMTP</td>
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<tr>
<td>12:10 PM</td>
<td><strong>Speaker Presentations (5 minutes each)</strong></td>
<td>Poonam Mishra, FDA</td>
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<td>Gregg Alton, Gilead</td>
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<td>Steven Pearson, ICER</td>
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<td>Donna Cryer, Global Liver Institute</td>
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<td>Michele Manos, Public Health Consultant</td>
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<td>David Ross, VA</td>
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<td>Mark Godwin, UnitedHealthcare</td>
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<tr>
<td>12:50 PM</td>
<td><strong>Panel Discussion</strong></td>
<td>Moderator: Sean Tunis, CMTP</td>
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<tr>
<td>1:10 PM</td>
<td><strong>Q&amp;A with Audience (please use the chat feature to submit questions)</strong></td>
<td>Moderator: Sean Tunis, CMTP</td>
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<tr>
<td>1:30 PM</td>
<td><strong>Adjourn</strong></td>
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WEB CONFERENCE AGENDA CONT’D

• Speakers will focus on what types of additional evidence would be most helpful to inform decisions by patients, payers and providers

• We welcome suggestions from speakers on potential strategies and approaches that would enable the production of new evidence most efficiently
SPEAKERS

Poonam Mishra, MD
Medical Officer, Division of Antiviral Products
U.S. Food and Drug Administration

Gregg Alton, JD
Executive Vice President
Corporate and Medical Affairs
Gilead

Steven Pearson, MD, MSc
President
Institute for Clinical and Economic Review

Donna Cryer, JD
President & CEO
Global Liver Institute

Michele Manos, PhD, MPH, DVM
Public Health Consultant (former Director of the Kaiser Permanente Viral Hepatitis Registry)

David Ross, MD, PhD, MBI
Director
HIV, HCV, and Public Health Pathogens Programs
Office of Public Health/Clinical Public Health
U.S. Department of Veterans Affairs

Mark Godwin, PharmD
Manager of Clinical Pharmacy
UnitedHealthcare
BACKGROUND

- Chronic hepatitis C affects estimated 130-150 million worldwide; 3.2 million in US.
- Associated with serious liver problems; leading cause of liver cancer and liver transplantation.
- In recent years, hepatitis C has surpassed HIV/AIDS as a cause of death.
- Treatment: up to 48 weeks of therapy; serious side effects, risk of drug-drug interactions, and burdensome dosing requirements.
• Sovaldi (sofosbuvir) approved through breakthrough drug pathway
  • must be intended to treat a serious condition, and
  • must have preliminary clinical evidence that the drug may demonstrate substantial improvement on a clinically significant endpoint over available therapies.
• Approval based on high rates of viral clearance and relatively low risks of side effects
• Shorter treatment duration, for some patients without interferon
• Additional all-oral Hepatitis C medications expected to receive approval through breakthrough pathway later this year
SPEAKER PRESENTATIONS

Poonam Mishra, MD  *U.S. Food and Drug Administration*
Gregg Alton, JD  *Gilead*
Steve Pearson, MD, MSc  *ICER*
Donna Cryer, JD  *Global Liver Institute*
Michele Manos, PhD, MPH, DVM  *Public Health Consultant*
David Ross, MD, PhD, MBI  *U.S. Department of Veterans Affairs*
Mark Godwin, PharmD  *UnitedHealthcare*
Hepatitis C Drugs – Evidence to Demonstrate Safety and Efficacy

Poonam Mishra, MD
Medical Officer
Division of Antiviral Products
U.S. Food and Drug Administration

CMTP/ICER Web Conference
July 7, 2014
Disclaimer

The views expressed in this presentation are those of the speaker and not necessarily official policy of the Food and Drug Administration.
Primary Efficacy Endpoint

• Primary Endpoint: Sustained Virologic Response (SVR)
  – Lack of detection of HCV RNA in blood 12 weeks after completing treatment (SVR12)
  – SVR correlated with improved clinical outcomes such as decreased HCC, hepatic events, fibrosis, all-cause mortality
  – Considered a virologic cure of chronic HCV
Rationale for HCV Trial Designs

• Single-arm trials using a historical control
• Immediate-versus-deferred placebo controlled
• Dose or treatment duration comparison
• Once interferon-free DAA regimens become available - an active-controlled superiority or noninferiority trial design may be preferred
Specific Populations

- Evaluation of DAA HCV regimens in patient populations with unmet medical need, such as:
  - Pre- and post- liver transplant subjects
  - Subjects with decompensated cirrhosis
  - Subjects with bleeding disorders
  - Subjects using intravenous drugs
  - Subjects on opioid maintenance therapy
  - Subjects with renal insufficiency
  - HCV/HIV-1 co-infected subjects
Post-Approval

• Optimizing regimen/duration for “harder-to-treat” subgroups identified in Phase 3 trials
• Tailoring an optimal regimen based on patient characteristics to identify patients who can be effectively treated with shorter regimen
• Data on populations underrepresented in Phase 3 trials
• “Real-world” effectiveness and safety data
HEPATITIS C DRUGS - EVIDENCE TO DEMONSTRATE EFFECTIVENESS & VALUE

Gregg Alton, JD
Executive Vice President
Corporate and Medical Affairs
Gilead
Steven D. Pearson, M.D., M.Sc.
President
Institute for Clinical and Economic Review
The California Technology Assessment Forum (CTAF)

• Major program of ICER
• Funded by Blue Shield of California Foundation
• ICER and UCSF faculty produce evidence reviews on effectiveness, cost-effectiveness and budget impact
• Independent panel of clinicians and public members meets in public to discuss the review, to vote on the evidence
• With input of Policy Expert Roundtable, recommendations made for applying evidence to improve practice and policy
CTAF Deliberation on New Drugs for Chronic Hepatitis C

• Evidence limitations noted
  – Criticism of size and the lack of randomized trials against active comparators or placebo
  – Existing trials of relatively short duration, thus not able to capture development of viral resistance
  – Concern about ability to identify subpopulations who benefit more/less from treatment
  – Concern that outcomes with clinical trial patients (and clinicians) will not reflect real-world outcomes
CTAF Deliberation on New Drugs for Chronic Hepatitis C

• Votes
  – Evidence is adequate to demonstrate superiority of the new drugs with nuance for certain subpopulations and regimens
  – New drugs represent a “low value” to Medicaid health systems because the budget impact would displace other care and/or limit access
Most Important Evidence Needed

1. Basic epidemiology of untreated HCV in diverse populations – how to identify patients who will do “well” with watchful waiting
   - Long-term patient databases
2. Long-term outcomes of patients achieving SVR: do cancer rates revert to baseline?
   - Long-term patient databases
3. Real-world SVR rates with enough patient information to facilitate robust indirect comparisons
   - Observational data
4. RWE on side effects and viral resistance
   - Observational data
5. Prospective trials of monitoring for patients who opt for no treatment: liver biopsies vs. non-invasive approaches
   - Pragmatic RCTs vs. observational designs
Hepatitis C Drugs: Evidence to Demonstrate Effectiveness & Value

GPC & ICER Web Conference July 7, 2014
Presenter: Donna R Cryer, JD
President & CEO, Global Liver Institute
Determining Clinical Effectiveness

- U.S. Food & Drug Administration
- American Association for the Study of Liver Diseases
- Infectious Disease Society of America
- International Antiviral Society – USA
- Post-Market Surveillance/Clinical Data from LHS
- Comparative Effectiveness Research (Head-to-Head Trials)
### Defining Value

Healthcare Outcomes Achieved per Dollar Spent

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Investment</th>
<th>Savings</th>
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<tbody>
<tr>
<td>Improvement Quality Adjusted Life Years</td>
<td>Hep C Drug Cost</td>
<td></td>
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<tr>
<td>Increased SVR (Cure)</td>
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<td></td>
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<tr>
<td>Increased Adherence</td>
<td></td>
<td>Less Resistance Development</td>
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<tr>
<td>Reduced Adverse Events</td>
<td></td>
<td>Less EPO, Chemotherapy, Home Care, Lost Income (patient/family caregiver)</td>
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<tr>
<td>Reduced Progressive Disease</td>
<td></td>
<td>Less Hospitalization, Imaging, Liver Cancer Medication, Transplant</td>
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<tr>
<td>Reduction in Absenteeism</td>
<td></td>
<td>Increased Productivity, Lower Turnover/Replacement Costs</td>
</tr>
<tr>
<td>Reduction in Presenteeism</td>
<td></td>
<td>Increased Productivity, Economic Growth</td>
</tr>
</tbody>
</table>
M. Michele Manos, PhD, MPH, DVM
Public Health Consultant

Formerly:
Director of Kaiser Permanente Viral Hepatitis Registry

Dr. Manos has received viral hepatitis research funding from Gilead Sciences, Vertex, and Merck.
Selecting the “right” HCV drug regimens: things we need to know

What are the real-world attributes of specific drug regimens?

Things are not what they seem in clinical trials. Large population based studies in non-academic settings are crucial.

*(E.g. crude SVR rates are about 50% with TVR and BOC)*

Data from baby boomers (now age 50-70) are essential, as that group should be the (urgent) main target.

- SVR rates
  - by age, disease, race, Rx history, host and viral genetics
- Side effects (prevalence, severity, cost, d/c rate)
  - which side effects are attributable to IFN versus RBV?
- Duration of treatment (flexibility, effectiveness)
- Long term relapse rates
  - *in the absence of immune stimulation (IFN), do we risk suppression rather than cure?*
Selecting the “right” HCV drug regimens: (more difficult) things we need to know

Can we quantitate the long term benefits of treatment?
Again, this should be assessed in community-based settings.
  • How do they vary by patient characteristics?
  • Does everyone benefit?
  • Does impact “drop off” at some age or disease state?

Who needs treatment, and when?
  • Factors considered: disease status, additional risk factors, age
  • Is there an “ideal” time to treat? A breakpoint in natural history?
  • Is there a subset of patients who will never progress, and thus less requirement for therapy?
  • Is there an upper age limit for treatment?
Selecting the “right” HCV drug regimens: an extremely large challenge

As is often the case, we must determine how to best distribute limited resources.

And at this time, we have limited information upon which to base those decisions.

Population health perspectives and decisions are distinct from clinical choices about treating individual patients.

However, if we don’t act soon, the huge majority of patients will simply age out of the window for intervention.

Many will die of liver disease.
Hepatitis C Drugs - Evidence to Demonstrate Effectiveness and Value

David Ross, M.D., Ph.D., M.B.I.
Director, HIV, HCV, and Public Health Pathogens Programs
Office of Public Health/Clinical Public Health
U.S. Department of Veterans Affairs
Disclaimer

The views expressed are those of the author, and do not necessarily represent the policy or opinion of the US Department of Veterans Affairs, the Veterans Health Administration, or the US Government.
HCV is a major clinical and public health issue for VA

![Chart showing prevalence of HCV antibodies]
Current VA approach to DAAs

- Cost is not a factor in treatment decision-making
- New DAAs added to VA National Formulary (Mar 2014)
- Updated VA HCV treatment guidelines (Apr 2014)
- Monitoring of drug uptake and outcomes (ongoing)
- Treatment of comorbidities
- Provider education (ongoing)
- Data feedback (ongoing)
Uptake of new HCV drugs in VA

Comparison of Simeprevir and Sofosbuvir Uptake in 2014 to Boceprevir and Telaprevir Uptake in 2011 Once Available in VHA

Data through 4/25/2014
VHA Population Health

BOC, boceprevir; TVR, telaprevir; SIM, simeprevir; SOF, sofosbuvir
Questions of interest to VA

• Access
  – How do we improve access to HCV treatment for Veterans with geographic barriers?
  – How do we redesign care to increase capacity?

• Quality
  – What is the real-world effectiveness of DAAs?
  – What is comparative effectiveness of different DAAs
  – What factors (patient, provider, system) predict adherence?
SCAN-ECHO and access

- Primary Colorado HCV treatment site: Denver VA
- Median patient travel ~50 miles.
- 3 SCAN-ECHO sites added:
  - Fort Collins
  - Grand Junction
  - Colorado Springs
- Median patient travel decreased to 19 miles
**In silico** comparative effectiveness

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Multivariate models for prediction of SVR in patients treated with peginterferon/ribavirin and either boceprevir or telaprevir</th>
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<tbody>
<tr>
<td></td>
<td>IPTW Odds ratio (95% CI) n = 835</td>
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<tr>
<td>Telaprevir (ref. Boceprevir)</td>
<td>1.57 (1.10–2.25) 0.01</td>
</tr>
<tr>
<td>African American (ref. All other)</td>
<td>0.80 (0.57–1.11) 0.18</td>
</tr>
<tr>
<td>Cirrhosis (FIB-4&gt; 3.25)</td>
<td>0.48 (0.34–0.67) &lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.83 (0.59–1.18) 0.29</td>
</tr>
<tr>
<td>Null response (ref. Naïve)</td>
<td>0.24 (0.14–0.43) &lt;0.0001</td>
</tr>
<tr>
<td>Partial response (ref. Naïve)</td>
<td>0.66 (0.42–1.03) 0.07</td>
</tr>
<tr>
<td>Relapse (ref. Naïve)</td>
<td>1.42 (0.95–2.14) 0.09</td>
</tr>
</tbody>
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CI, confidence interval; IPTW, inverse probability-of-treatment weighting; ref, reference; SVR, sustained virological response.

Other questions

• **Hepatitis C-specific lessons**
  - Can patients with traditional barriers to treatment (IDU, EtOH use) be treated successfully?
  - Does SVR achieved through DAAs carry the same clinical benefit as SVR achieved through PEG-Riba?
  - What is the utility (e.g., in terms of net QALY changes) for treatment of different populations?
  - Any prevention benefits (decreased transmission, post-exposure prophylaxis)/

• **General lessons learned**
  - Public health: Can interventions to increase access be extrapolated to other therapeutic areas with large caseloads without sacrificing quality?
  - Drug development/regulators: What are the pro’s/con’s of this drug development model for other therapeutic areas (e.g., Abx)?
  - Payors: Better mechanisms to anticipate/project costs of expensive new agents? Does traditional cost-effectiveness modeling apply well with large populations?
Questions?

- David.Ross4@va.gov
- publichealth@va.gov
- www.hepatitis.va.gov
HEPATITIS C DRUGS - EVIDENCE TO DEMONSTRATE EFFECTIVENESS & VALUE

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Manager of Clinical Pharmacy
UnitedHealthcare
HEPATITIS C DRUGS - EVIDENCE TO DEMONSTRATE EFFECTIVENESS & VALUE

- Long-term SVR12 durability data
- Comparative studies designed to identify the most effective direct acting agent (DAA) combinations based on patient characteristics, disease staging and regardless of manufacturer sponsor
- Include both comparative clinical outcomes, intermediate and long-term, as well as comparative cost outcomes
- Additional data on specific subtypes of hepatitis C and subpopulations of interest
RECOMMENDATIONS FOR FUTURE RESEARCH EFFORTS:

Studies designed to determine when to initiate treatment

• Long term data and outcomes for patients achieving SVR12/SVR24 based on fibrosis score at time of treatment initiation (e.g. long-term liver-related complications, all-cause mortality, etc. when comparing patients who achieve SVR when therapy is initiated at F1 vs. F2 vs. F3 vs. F4)

• Research must highlight degree of fibrosis at time of treatment initiation so stakeholders can determine when it would be best, and most cost-effective, to initiate treatment

Pharmacoeconomic studies designed to demonstrate the true value of DAA treatment regimens

• Should include both pharmacy costs as well as medical cost savings

• Post marketing studies or a registry database to track long-term medical cost savings

• Must consider the all-in costs of treatment including comparative cost-effectiveness of each drug and drug combination, as well as those respective costs in relation to medical costs and medical cost savings
Panel Discussion

Moderator: Sean Tunis, CMTP
Please use the **chat feature** to type and submit your questions. The webinar facilitator will share your question with the audience, and ask the speakers to respond.

We will do our best to respond to everyone, but our time may be limited.
Thank You For Participating!

For more information about this web conference or CMTP’s Green Park Collaborative, please email Els Houtsmuller: els.houtsmuller@cmtpnet.org

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