HCV addendum to the DUR Board meeting information packet for April 16, 2014 meeting:

The MED Project prepared a report at the request of AR Medicaid and another state Medicaid agency evaluating the available data on Sofosbuvir and the AASLD Guidelines, Sofosbuvir *for the Treatment of Hepatitis C and Evaluation of the 2014 American Association for the Study of Liver Diseases Treatment Guidelines.*

The MED Project was established at the Center for Evidence-based Policy at Oregon Health & Science University in Portland, Oregon in 2006 as a self-governing collaboration of state Medicaid agencies and their partners. MED's mission is to provide policy-makers with the tools and resources they need to make evidence-based decisions. MED's primary purpose is to improve decision making in Medicaid programs by:

- Producing independent and objective evaluations of clinical evidence to inform decisions made by policy-makers, purchasers, providers, and consumers.
- Sharing best practices and engaging in collaborative problem-solving to accelerate improvements in healthcare outcomes and health system efficiency.
- Supporting state efforts to increase transparency and evidence-based decision making in state health coverage policies.

The MED project report analyzed seven peer-reviewed publications which covered ten studies of Sofosbuvir treatment. This analysis included completed trials with published reports. Studies included in this analysis are: Gane 2013; Jacobson 2013; Kowdley 2013; Lawitz 2013a; Lawitz 2013b; Osinusi 2013; Rodriguez-Torres 2013.

Below are excerpts of the MED project report evaluation on Sofosbuvir and the AASLD guidelines, and some sections have added yellow highlight:

> **Treatment Effectiveness**
> Nine of ten studies reviewed enrolled patients with HCV-1 (n=889), five included those with HCV-2 or HCV-3 (n=1060) and two studies also included patients with HCV-4, -5, or -6 (n=41).
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> Studies tended to include populations with favorable prognostic factors. Fewer than 10% of total enrolled populations were African or African American. Slightly over 13% had cirrhosis. No subjects with concurrent hepatitis B or HIV infections were included in published studies..
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> All studies were rated as having a high risk of bias with the exception of the comparative phase II National Institutes of Health (NIH) sponsored study by Osinusi (2013) which was rated as being at moderate risk of bias.
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> Eight of 10 studies did not have a true comparator (e.g., single arm, dose or duration varying studies) and some used an invalid comparator (e.g., comparator not standard dose or standard of care). No study of sofosbuvir in HCV-1 populations compared the drug to current standard of care, which is triple therapy including PEG-INF + RBV with boceprevir or telaprevir. Most studies were open label and all but one (Osinusi 2013) were funded and controlled by the drug's manufacturer. Most study arms included few patients, especially among subgroups of particular interest to public payers, and duration of follow-up was limited with no study

reporting primary outcomes at more than 24 weeks after the end of treatment. Most studies were multi-centered and eight studies enrolled 10 or fewer patients per site. None of these studies reported results by study center.

Research Pipeline

As of March 7, 2014, there were 53 studies registered on clinicaltrials.gov that include the drug sofosbuvir. The majority of the studies are similar to the studies reviewed in this report in that they compare different doses of sofosbuvir or vary duration of treatment in defined populations. No registered studies compare a sofosbuvir-based regimen with current standard of care (e.g., interferon based double or triple therapy). All but four of the studies are sponsored by sofosbuvir's manufacturer, Gilead Science, and the other trials are sponsored by Bristol Myers (three trials combining sofosbuvir and daclatasvir) and the University of Florida with Vertex Pharmaceuticals (sofosbuvir combined with telaprevir)…

In summary, there are no studies registered in clinicaltrials.gov which compare sofosbuvir based treatment to the current standard of care, there is no forthcoming evidence on sofosbuvir, interferon, and ribavirin treatment in genotype 1 patients who have failed previous treatment, and there are no registered studies being conducted by anyone other than pharmaceutical companies.

Guideline Assessment

The only identified guideline addressing the use of sofosbuvir is published by the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) Hepatitis C Guidance (AASLD 2014). The AASLD/IDSA Hepatitis C Guidance included 27 recommended treatment regimens based on genotype, prior treatment, and co-morbid conditions and nine alternative treatment regimens. All 27 recommended regimens include sofosbuvir except in patients with severe renal impairment.

The overall quality of the guidance was rated poor and not evidence-based by two independent raters Two areas raised the greatest concern. First, there were no assessments of risk of bias or quality for individual studies or the overall strength of the evidence cited for each recommendation. The published studies cited in the AASLD/IDSA Guidance as supporting the efficacy of sofosbuvir are described in other sections of this report. As noted above, nine of the 10 published studies (Gane 2013; Jacobson 2013; Kowdley 2013; Lawitz 2013a; Lawitz 2013b; Rodriguez-Torres 2013) were rated as poor quality, with one study (Osinusi 2013) rated as fair quality.

Second, there is substantial risk of conflict of interest influencing the recommendations from both individual panel members and funding source. For example, four of the five panel chairs had financial relationships with Gilead Science, as did 15 of the 21 panel members. Although members were given the "opportunity" to divest and recuse themselves from discussions or be recused by the chair, there was no description of when or how this occurred. More important, the International Antiviral Society-USA (IAS-USA) was the collaborating partner for development of the guidance. It was "responsible for providing expertise and managing the [p]anel and the [g]uidance development process", and one of the five panel chairs was from

this society. Funding for the IAS-USA is primarily from the pharmaceutical industry including Gilead Science.

In summary, the ASSLD/IDSA Guidance was found to be of poor methodological quality as its findings were based on poor quality evidence and the authors and sponsors of the guidance had multiple and significant conflicts of interest.
[Side note: The applicability rating was also rated as “poor”.]

Who to Treat and When to Treat
In general, patients at greatest risk of progressing to cirrhosis have detectable HCV-RNA and liver histology demonstrating fibrosis as defined by Metavir fibrosis stage 2 or greater (portal fibrosis with few septa – see Table 5 below). In fact, the current AASLD-IDSA Guidance (AASLD 2014) states that "it may be advisable to delay treatment for some patients with documented early fibrosis state (F 0 to 2), because waiting for future highly effective, pangenotypic, DAA combinations in INF-free regimens may be prudent."

Summary bullets from the MED Project Report:
Potential criteria to guide the use of sofosbuvir could be developed that is consistent with currently published studies. Listed below are several factors to consider.
• Not use sofosbuvir as monotherapy;
• Require a liver biopsy within the past three years;
• Treat only patients at greatest risk of progressing to cirrhosis (e.g., Metavir fibrosis stage greater than or equal to 2 and additional factors increasing risk of progression to cirrhosis [hepatic steatosis, men, older, elevated serum alanine transaminase, greater hepatic inflammation]);
• Exclude use in patients with alcohol or drug use within the past year, significant cardiac or pulmonary disease, uncontrolled hypertension or diabetes, seizure disorder, renal disease (estimated glomerular filtration rate less than 60mL/min).

Although improved treatments for HCV are certainly desirable, the long course of disease progression also makes it incumbent upon policymakers and clinicians to make sure that treatments will be effective. Most currently infected patients have time available to wait for conclusive data on the effectiveness and harm profile of sofosbuvir or other new drugs before deciding on an optimal treatment regimen.

This rapid evidence review located 10 studies published in seven articles, although the majority of them were non-comparative studies and all but one was at high risk of bias. There were two comparative studies of sofosbuvir treatment for HCV-2 and HCV-3 infection, but no comparative studies for the treatment of HCV-1. Currently available studies do not provide sufficient evidence for the effectiveness of sofosbuvir-containing regimens for the treatment of HCV-2 and -3, and no adequate information on the treatment of HCV-1 infected individuals. While initial, uncontrolled, response rates appear to be relatively high among carefully selected populations, response rates in “real world” populations are likely to be much lower. Furthermore, there is evidence that relapse rates may be substantial (approximately 20 to 30%), even among patients who are fully treated with these regimens. Similarly, adverse effects have not been studied in large numbers of patients and among those with substantial

other risk factors for harms. When the first two protease inhibitors began to be used in clinical practice, the risks of adverse events approximately tripled and there could be a similar concern with these even newer drugs as they are used in widespread clinical practice.

The recently published HCV treatment guideline published by AASLD and IDSA is of poor methodologic quality and does not adhere to international or US standards for guideline development. In addition, guideline authors had substantial and multiple conflicts of interest. The evidence supports that few, if any, patients should be treated with this drug at this time. While awaiting more and better evidence on sofosbuvir, policymakers may decide to not allow use of or to allow very limited use of this drug. If limited use is contemplated this report details factors to consider, such as limitation to use in carefully selected HCV-2 and -3 infected individuals who are at great risk of shortly progressing to cirrhosis, and only as part of a RBV containing regimen. Policymakers, clinicians and patients should remain aware of upcoming drug research and carefully examine the quality of new research as it is made available.

And below is a paper discussing the differences of SVR12 and SVR24.

Thorlund K, Druyts E, Mills EJ. "SVR12 is higher than SVR24 in treatment-naive hepatitis C genotype 1 patients treated with peginterferon plus ribavirin." Clinical Epidemiology 2014; 6: 49-58. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0062837/

The conclusion of the above paper: "Considering the relatively large difference observed between SVR12 and SVR24, it seems reasonable to insist that future clinical trials report both outcome measures to allow for complete transparency and clarity in their interpretation."

Summary After Review Of All Available Data…

- There is a lack of follow-up data and relapse rates from the Sofosbuvir clinical trials; more data are needed in order to make long-term recommendations on the use of Sofosbuvir, including needing SVR-24 data;

- There are no comparative studies with the current triple therapy standard of care against Sofosbuvir for GT-1 treatment naïve patients;

- No studies have been peer reviewed and published with Sofosbuvir for GT-1 treatment experienced who relapse or non-responders, etc. COSMOS is unpublished trial, and although it is getting a lot of media attention, there are no meaningful control arms;

- For GT-1 cirrhotic patients, comparative trials of sofosbuvir thriple therapy against boceprevir and/or telaprevir triple therapy are needed. Boceprevir resulted in a 52% SVR24 in metavir 3-4 in Poordad, et al.. Telaprevir was also effective in cirrhotics, tx-naïve in Jacobson, et al. With not knowing the true difference between SVR12 and SVR24 in this population, it may be true there may be no difference between these SVR response rates and the boceprevir and telaprevir may be just as effective.

- For patients in GT-2 and GT-3 who previously failed therapy (relapsers, non-responders) or patients in whom peg-interferon is contraindicated, although the relapse rates with Sofosbuvir appeared high, the FUSION trial provides data to suggest use of sofosbuvir and ribavirin may be an option, especially if those patients are too sick to wait for the next generation of drugs to hit the market over the next year (GT-2 (for 12 weeks) or GT-3 (for 24 weeks) who did not achieve SVR24 with prior interferon therapy).

- For the co-infected patients with HIV and HCV, the HIV data was in trial without any control arm and is not yet published (PHOTON-1). There are ongoing trials with control arms with boceprevir and telaprevir (Lancet Infect Dis 2013; 13: 597–605 and Ann Intern Med. 2013;159:86-96, respectively.)

- Relapse rates are largely unknown from the Sofosbuvir trials but some of the trials do indicate high relapse rate; relapse of Sofosbuvir patients may make them ineligible for future treatments, some of which are expected to be out end of 2014 or early 2015;

- Guidelines: other organizations in the U.S. are also questioning the use of the guidelines because the guidelines used poor methodological quality as its findings were based on poor quality evidence and the authors and sponsors of the guidance had multiple and significant conflicts of interest (15 out of 21 authors have COI, and 4 out of 5 panel chairs had financial relationships with Gilead);

- “Historically, Phase II and Phase III clinical trials of hepatitis C virus (HCV) treatments have defined sustained virological response (SVR) as an undetectable HCV RNA 24 weeks after end of treatment (SVR24). This definition of SVR has been used in all key randomized clinical trials (RCTs) of peginterferon plus ribavirin, telaprevir, and boceprevir.” However, with the newer direct acting agents (DAAs) (eg, faldaprevir, simeprevir, and sofosbuvir), clinical trials assessing these treatments have used SVR at 12 weeks after end of treatment (SVR12).

- The “historical SVR control rate of 60%” cited in Sofosbuvir trial was an adjusted number (downward, from 65% to 60%) for the Neutrino study. The Fission study for Genotype (GT)-2 & GT3 showed PEG + RBV effectiveness to be GT2= 81% and GT3= 71% for non-cirrhosis, and GT 2=62% and GT3=34% with cirrhosis. The Sofosbuvir patients in that trial had high relapse rates of 48% after 12 weeks of Sofosbuvir + RBV treatment. Data from a clinical trial “Peginterferon-α2a and Ribavirin Combination Therapy in Chronic Hepatitis C” showed better SVR24 rates for GT2 and GT3 ranging from 83% - 85% for low viral load patients and 80% - 84% for high viral load patients.

- The lack of trials comparing sofosbuvir to the standard of care (either triple therapy) is remarkable. The measurement of SVR12 instead of SVR24 should be noted to be relatively

higher with SVR12 than with 24 in a homogeneous population, contrary to the population (mixed GT2 1, 2, 3's) used to allow sofosbuvir to report only SVR12).

- Marketing of convenient dosing and ease of route of administration should not replace importance of effectiveness and follow-up data (rate of relapse and SVR-24);

- Future pipeline shows several more HCV drugs due within the year;

- Excessive cost of Sofosbuvir® in addition to costs of other drugs with the treatment;
  EAC for Sofosbuvir =$1032 per tablet = 12 weeks of Sofosbuvir treatment = $86,688

- There is an ongoing open label single arm Phase-III study (RESTORE) assessing the efficacy of simeprevir in treatment-naïve and treatment-experienced patients with genotype 4 HCV, however, no data are available at this time.

- EAC Olysio® (simeprevir) = $815.28 ea capsule; 12 wks of Olysio= $68.483.52

HCV PROPOSAL:

1. Current treatment for GT-1 of triple therapy of Peg + RBV + boceprevir (Victrelis®) or telaprevir (Incivek®) will remain available under current criteria.
2. GT-2, GT-3, and GT-4: Current treatment of Peg + RBV will remain available under current criteria.

Criteria PROPOSAL to Approve Sovaldi® (sofosbuvir) until more data is available:

1. GT-1: Treatment Naïve: Stage 4 Cirrhosis will be reviewed on a case-by-case basis;
2. GT-1, GT-2, GT-3: Pre-transplant patients reviewed on a case-by-case basis (treatment naïve or relapse or non-responder); there is currently no data to suggest boce-/tela- triple therapy would be any worse than sofosbuvir triple therapy, however the shorter 12 week duration of therapy may be of importance on the transplant list with the sofosbuvir therapy regimen.
3. GT-2 and GT-3: Only relapse or non-responder to current standard of treatment of PEG and RBV will be reviewed on a case-by-case basis;
4. All Genotypes: Any requests for "intolerance" or "allergy" to Peg-interferon will be reviewed on a case-by-case basis.
5. All other requests will be reviewed on a case-by-case basis.

Criteria PROPOSAL to Approve Olysio® (simeprevir):

1. GT-1: medical necessity reviewed on a case-by-case basis (as is telaprevir);

2. Requests for GT-4 will be reviewed on a case-by-case basis. Simeprevir has an ongoing efficacy study with simeprevir + PEG + RBV in GT-4 treatment naïve and treatment experienced patients and the data will be reviewed when available.\

References

(Gane 2013; Jacobson 2013; Kowdley 2013; Lawitz 2013a; Lawitz 2013b; Osinusi 2013; Rodriguez-Torres 2013)

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Kowdley, K., Lawitz, E., Crespo, I., Hassanein, T., Davis, M., & DeMicco, M. (2013). Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naïve patients with hepatitis C genotype 1 infection (ATOMIC): An open-label, randomized, multicenter phase II trial. *The Lancet, 381*(9883), 2100-2107.

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