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CALIFORNIA TECHNOLOGY ASSESSMENT FORUM℠

The Comparative Clinical Effectiveness and Value of Simeprevir and Sofosbuvir in the Treatment of Chronic Hepatitis C Infection

Summary of Public Comments and Response on Draft Report

April 15, 2014

Response to Public Comments

The Institute for Clinical and Economic Review (ICER) produces publicly-available evidence reviews for consideration by the California Technology Assessment Forum (CTAF). As part of this process, ICER welcomes public comment from individuals and organizations on its proposed project scope, voting questions, and evidence assessment. All comments are separately reviewed by each member of the research and leadership team and then discussed prior to any decisions on revisions to the scope, voting questions, and/or evidence assessment. For transparency, all those submitting comments during the public comment period are acknowledged in this response document. However, detailed responses are focused on those comments pertaining to the project scope, evidence assessment, and major assessment findings.

This document responds to comments on the draft report from the following parties:

- Sammy Saab, MD, MPH, AGAF, Professor of Medicine and Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA
- Robert G. Gish, MD, Robert G. Gish Consultants, LLC, San Diego, CA
- Lisa M. Nyberg, MD, MPH, Southern California Permanente Medical Group, San Diego, CA
- Gerald N. Rogan, MD, Rogan Consulting, Sacramento, CA
- Donald M. Jensen, MD, University of Chicago Medicine, Co-Chair, AASLD-IDSA HCV Guidance, Chicago, IL
- Catherine Frenette, MD, Medical Director of Liver Transplantation, Scripps Center for Organ Transplantation, La Jolla, CA
- Camilla S. Graham, MD, MPH, Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Boston, MA
- Paul J. Pockros, MD, Liver Disease Center, Scripps Clinic, La Jolla, CA
- Paul Justison, Oakland, CA
- Andrew Reynolds, Hepatitis C Education Manager, Project Inform, San Francisco, CA
- Rachel McLean, Viral Hepatitis Prevention Coordinator/STD Healthcare Policy Analyst, California Department of Public Health, Sacramento, CA
- Craig Ennis, MD (affiliation unknown)
- Christian B. Ramers, MD, MPH, Director, Graduate Medical Education – Assistant Medical Director, Family Health Centers of San Diego, San Diego, CA
- Gregg Alton, Executive Vice President, Corporate and Medical Affairs; and Hans Reiser, M.D., Senior Vice President, Medical Affairs, Gilead Sciences, Inc., Foster City, CA
- Richard K.P. Sun, MD, MPH, Chief, Clinical Programs, Policies, and Procedures Unit, Health Plan Administration Division, California Public Employees Retirement System, Sacramento, CA
- Connie Chiang, PharmD, Associate Director, Medical Information, Janssen Scientific Affairs, LLC

	Comment	Response
Sammy Saab, MD, MPH, AGAF, Professor of Medicine and Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA		
1	Transition rates before different stages of liver disease are based on a single study over a 12 years old, is generally wrong. The rates used underestimate the likelihood of disease progression. The cohort does not appear to develop complications at the same rate that occur in real life. This would underestimate the costs associated with liver complications.	*Thank you for your comments. We have acknowledged in the final report that estimates of disease progression and mortality vary. We have also conducted exploratory analyses in the model section in which complication rates are double those assumed in primary analyses. Findings from these analyses do not change the overall model conclusions, however.*
2	The SVR utilized in the model for genotype 1 patients is incorrect by almost 10% points. An incorrect lower SVR would underestimate the benefits of antiviral therapy. Indeed any model is very sensitive to estimates of treatment efficacy. If indeed the producers utilized a network analysis, did they realize that patients of the Neutrino study had many negative predictors of a sustained viral response? Thus, the SVR would have been even higher if applied to a different patient population.	*As noted in the review, SVRs for genotype 1 treatment-naïve patients were lower than those reported in individual studies because the network meta-analysis is focused on the comparative effects of active treatment vs. control therapy, allowing for statistical pooling of data from studies with populations that differ in terms of both patient characteristics and treatment efficacy. Because nearly all studies (including NEUTRINO) were uncontrolled, however, we were forced to impute the SVR for PR in a hypothetical PR control group for sofosbuvir using data from the PR control group of the only randomized sofosbuvir trial in this population. We acknowledge this limitation in the report.*
3	The Costs of Liver Complications were lumped together into a single value of approximately $20k. This value is based on single study of Florida Medicaid Patients. This number is inconceivable when we consider the costs of treating complications of cirrhosis such as variceal bleeding, encephalopathy, and liver cancer. The cost of being in the hospital can be $2-5k/day, and in an ICU $5-10k/day. This number is in complete contrast to that reported by other well designed Gordon and McAdams et al using national databases. Thus, this inaccurate underestimate the costs of not curing hepatitis C.	*Two changes have been made to the final report. First, we clarify that our primary estimate of the costs of liver-related complications were applied to <u>each</u> year of follow-up; in reality, many events would occur toward the end of each timeframe, and costs would only accrue once the events occur. Second, we conducted an alternative analysis using the Gordon estimate for attributable costs of end-stage liver disease (approximately $42,000 per year). This results in a small increase in cost offsets but does not change overall model findings.*
4	The assumptions of number of patients to be treated is also incorrect. The current model assumes that 50-75% of HCV patients know they are infected. This is impossible given that less than a third of patients even know they are infected. In no treatment of any disease state is there a treatment rate of 50% achieved. Indeed, over the past 15 years less than 10% of infected patients have treated. It is inconceivable that this likelihood will over triple when most patients do not even know they are	*We believe that there are potentially countervailing effects at work here, given well-publicized efforts to increase screening for disease and the availability of treatment for those who had been without options previously. Nevertheless, we produced an additional analysis for the final report (which can be seen in the Appendix) that assumed that 25% of patients with chronic hepatitis C would be aware of their infection and present for treatment.*

	infected. Furthermore, not everyone with hepatitis C should be treated. Study after study have shown that most benefit is obtained from curing HCV in those patients with advanced fibrosis. Assuming 50% of patients are treated is unrealistic, unwarranted, and not necessary. The strategy of treating everyone would significantly incorrectly increase the overall costs of treatment.	*We agree that there might be differential effects of treatment in patients with advanced fibrosis and so structured our economic analyses to accommodate this in the report.*
5	The impact of Q80K should not have been ignored. Of the two hepatitis C 1 genotype subtypes, 1a is the most common. Approximately 30% of patients with genotype 1a have the mutation. Patients with Q80K get no benefit from the addition of simeprevir to interferon and ribavirin.	*The effects of Q80k were not ignored. Use of simeprevir is not recommended in patients with this mutation, and so we produced estimates of simeprevir's performance in patients without Q80k. The budget impact analysis also took the proportion of patients with Q80k who would not be eligible for simeprevir into consideration.*
6	Others – managing adverse effects, work productivity, and quality of life are not considered in the model.	*We have already acknowledged these limitations in the report.*
Robert G. Gish, MD, Robert G. Gish Consultants, LLC, San Diego, CA		
1	I would like to ask the CTAF to reconsider the statistics which were used in the recent document released from the meeting in San Francisco on March 10, 2014, concerning HCV treatment with the newly FDA-approved agents. I think it is clear that each epidemiological study that has been published with prevalence estimates has strengths and weaknesses. As the CDC has acknowledged, the NHANES data used as a large part of the basis for the CDC estimate of CHC prevalence in the U.S. underrepresents populations that may be at increased risk for HCV infection such as incarcerated and homeless persons and people on active military duty. In addition, the CDC has noted that multiple smaller racial/ethnic groups (including Native Americans, Alaskan Natives, and Asians), shown by a number of studies to potentially have higher rates of infection, are not adequately represented. I hope that CTAF is making efforts to consider these populations in your calculations of HCV treatment costs with the new therapies.	*Thank you for your comments. Limitations on the NHANES data are acknowledged in the report. In addition, our budget impact analyses made adjustments to the estimated prevalence of hepatitis C in California by including estimates for incarcerated and homeless individuals, two of the key underrepresented groups that you describe.*
2	If we consider these recent studies, it seems very possible that there are at least 5 million people chronically infected with hepatitis C in the United States, 94-95% of whom have not yet been successfully treated, a population of 4,700,000 to 4,750,000 people in need of treatment. This would mean that some current estimates of future HCV-associated costs are a drastic underestimate of what	*We acknowledge variability in prevalence estimates in the final report.*

	the true costs will ultimately be. We believe that it is important to consider that the NHANES data used by the CDC substantially underestimates the true prevalence of CHC, and that showing broader ranges of prevalence data could expand opportunities for advocacy and awareness, as well as provide a solid basis for supporting that the treatment with the new HCV medications are even more cost effective and less expensive, with the cost to treat per "cure" in the $100,000 range, or approximately one-half the greater than $200,000 cost per cure with the previously approved protease inhibitors (references on file).	
3	Another major concern I have is the potential medico-legal consequences of mandating a liver biopsy prior to treatment or mandating that patients fail second-line treatment with the potentially serious complications of long-term interferon use (more than 12 weeks) and the known high rate of systemic complications of INF + Ribavirin + first generation protease inhibitors if used in patients with cirrhosis.	*While there may be medico-legal consequences, the information provided on coverage policies and prior authorization criteria suggest that such criteria are being employed by some payers. Our review did not advocate for any one position, but it did explore the potential economic impact of treatment in different patient subsets.*
Lisa M. Nyberg, MD, MPH, Southern California Permanente Medical Group, San Diego, CA		
1	In reference to my estimate of interferon ineligible or interferon intolerant patients (personal communication, Lisa M. Nyberg, MD, page 74), I would like to modify this figure. Since I spoke to Mr. Ollendorf, I have performed new analyses of this patient population. The data reveal that approximately 40% of those that know that they are infected with hepatitis C have a comorbid condition that could preclude treatment with interferon-based therapy.	*Thank you for your comments. We have changed this reference in the text of the final report and updated our budget impact analysis accordingly.*
2	Further, this population is more likely to be older and have other health conditions that predispose them to more advanced liver disease. These conditions include non alcoholic fatty liver disease, diabetes, cardiovascular disease and other comorbidities. This population would be expected to benefit greatly from treatment and cure of chronic hepatitis C.	*Thank you for your comments.*
Gerald N. Rogan, MD, Rogan Consulting, Sacramento, CA		
1	Limitation of coverage to selected degrees of liver impairment seems inappropriate and may be legally unenforceable. All patients with Hepatitis C infection are candidates for treatment. Medical but not cost limitations are applicable. Expected toxicity will self-limit unmotivated patients.	*Thank you for your comments. Please see our comment #3 to Dr. Gish above.*

Donald M. Jensen, MD, University of Chicago Medicine, Co-Chair, AASLD-IDSA HCV Guidance, Chicago, IL		
1	After attending the CTAF-ICER conference on HCV therapy online, I would like to clarify a few issues regarding the AASLD/IDSA HCV guidance document. Approximately one year ago, both the AASLD and IDSA governing boards approved grants of approximately $130,000 each to jointly sponsor a novel online, web-based practice guidance document for HCV therapy. No commercial or industry funding was used. IAS-USA was contracted to provide administrative support for the guideline, and this function was totally supported by the grants from the AASLD and IDSA. Again, no industry funds supported this activity of IAS-USA. Finally, 2 co-chairs from both AASLD and IDSA were appointed by the respective governing boards and a 5th cochair was appointed by IAS-USA. No chairperson currently has received personal honoraria from industry, and all have been free of industry conflicts for >12 months. Ten writing panel members were identified by each society governing board based upon their knowledge and expertise in hepatitis C; vetted by the co-chairs and an outside society leader; and their society conflicts of interest were reviewed by the entire panel. Additional panel members representing the CDC were invited for their particular expertise in HCV testing. The writing panels were initiated on October 6, 2013. 17 of 23 writing panel members have no current personal conflicts of interest with the HCV industry. Several panel members, however, have institutional research grants from industry clinical trials. For transparency, these conflicts have been posted under each panel member's name in the guidance document ever since the document was first available on January 29th. We will be adding a table of each member's conflicts to be more visible and easier to find.	*Thank you for your comments.*
Catherine Frenette, MD, Medical Director of Liver Transplantation, Scripps Center for Organ Transplantation, La Jolla, CA		
1	I heard that the California Technology Assessment Forum rated sofosbuvir as “low value” last week. This obviously was an error, as it has been well shown that patients with hepatitis C have an increased risk of death even before they develop cirrhosis, and that clearing the virus normalizes their life expectancy.	*Thank you for your comments.*

	While I realize that the cost of sofosbuvir is high, the fact that it cures a large number of patients with only 12 weeks of therapy actually ends up being cost effective. It prevents the high cost of care of patients with cirrhosis who then develop hepatocellular carcinoma even if the virus is cleared when cirrhotic. In addition, waiting to treat someone until they have cirrhosis decreases the effectiveness of the therapy, and continues to incur lifelong cost of these patients who require surveillance for hepatocellular carcinoma development and progression of their liver disease even for those who are lucky enough to clear virus. Determining that this medication is low value is short-sighted, and ensures that we will have an epidemic of patients with cirrhosis to care for over the next 15 years. Please reconsider your stance.	
Camilla S. Graham, MD, MPH, Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Boston, MA		
1	Table 1: "Die from cirrhosis or liver cancer = 1% – 5%". These data seem to imply that there is a 1 to 5% chance of someone ever dying of liver disease related to HCV. The CDC (Rein, Annals 2011) estimates that 37% of people with HCV infection will die of their HCV if no intervention/treatment is provided.	*Thank you for your comments. We have acknowledged variability in estimates of disease prevalence and progression in the final report and included additional citations such as the simulation model produced by Rein and colleagues.*
2	Section 3: Coverage Policies: The Massachusetts Medicaid program (MassHealth) has published guidelines for antiviral drugs used for hepatitis C, including prior authorization requirements.	*The coverage policies believed to be most pertinent to CTAF included those from California payers as well as national payers and PBMs.*
3	Page 27: "In addition, it is important to note that among patients with SVR, those with cirrhosis prior to treatment were still at risk for HCC during follow-up. Thus achieving an SVR24 will not prevent the complications of chronic HCV infection for all patients." This is an important point. The risk of HCC is reduced up to 80% if a patient with advanced liver fibrosis achieves SVR, but there is residual risk and these patients need life-long screening for HCC, which increases costs and patient distress. This should argue for treating people if they are diagnosed with HCV at the point they have developed cirrhosis, but not waiting to treat until someone has developed cirrhosis if they are diagnosed with HCV at a point where they have milder fibrosis.	*Based on the comments received, it appears that there are a variety of opinions on the most appropriate patients for antiviral treatment. In addition, the AASLD/IDSA guideline section on "in whom and when to initiate treatment" is forthcoming.*

4	Comments about Table 23: "TEL + PR (12/24) (pre-DAA)": About 1/3 of patients require 48 weeks of P/R	*We have added a sensitivity analysis to the final report in which 60% and 40% of TEL patients were assumed to receive 24 and 48 weeks of PR respectively. This did not change the primary model conclusions for genotype 1.*
	"SOF + PR (12) 830 SVR per 1000": The overall SVR in naïve genotype 1 patients is 90%, so why is this number so low?	*As described in the evidence section, the network meta-analysis for genotype 1 generated SVR rates in comparison to a common referent rate for PR alone. Please see sections 6.2 and 6.3 for further discussion of these results.*
	"SOF + SMV + R (12) 90% SVR, 50 discontinue for AE": Why is this estimate for early discontinuation nearly as high as the 55 estimated for SMV+P+R x 24 weeks? I have a number of patients with very advanced fibrosis, with and without HIV coinfection, who are on SOF+SMV+/-RBV and this regimen is very well tolerated. I expect that the discontinuation rate, especially for SOF+SMV, will be similar to SOF+RBV x 12 weeks. Registries such as TARGET should help us understand the real-world outcomes (SVR and AEs) with this regimen.	*This was an inadvertent transposition of the overall adverse event rate reported to date for the COSMOS study. To date, no patients have been reported to have discontinued due to adverse events in COSMOS. This has been corrected in the final report.*
5	Comments about Table 24: "TEL + PR (12/24) (pre-DAA), 700 SVR per 1000": Relapse patients have a higher SVR rate than overall naïve patients with DAA-containing regimens and should be averaged with naïve patients, not treatment experienced patients. Treatment experienced null responders (SVR 31%) would all have 48 weeks of P/R, not 24 weeks. Null responders +/- cirrhosis were the main group that was studied with SOF+SMV+/-RBV. If the appropriate comparison had been done, the costeffectiveness of SOF+SMV would be far greater.	*Trial reports were not consistent in providing subgroup results according to category of prior response, so we were forced to analyze all treatment-experienced populations together to allow for specification of the network meta-analysis. While the calculation was not explicitly performed in our sensitivity analyses, increasing the cost of TEL+PR to account for the proportion who received 48 weeks of PR would reduce SOF+SMV±R's cost per additional SVR from approximately $353,000 to $303,000.*
6	Page 75: "Drug costs to treat all these patients with the previous standard of care are estimated to total approximately $14 billion across all genotypes. Were these patients all treated instead with the most effective new regimen, treatment costs would grow by $18 billion to a total of $32 billion." Not taking retreatment costs into account makes this analysis nonsensical. One could argue that 24 weeks of standard IFN would be the cheapest approach,	*We understand the concern regarding retreatment; these costs were accounted for in our cohort models. The budget impact analysis, however, was intended to illustrate the immediate impact of making a wholesale switch to newer regimens (including a switch for patient subgroups who had no treatment options previously).*

	even though it only cures 6% of genotype 1 patients.	
7	Page 78: "….the costs per SVR generated in this analysis are generally higher than those previously published for telaprevir ($189,000), different regimens of PR ($17,000-$24,000)…" If one just takes into account the costs of the drugs (using WAC prices), which underestimates the costs associated with managing adverse events associated with IFN-based regimens, the cost per cure for genotype 1, naïve patients is quite similar [table presented]. Your analysis has grossly underestimated the cost per cure for P/R.	*In keeping with published standards for economic evaluation, we have calculated the cost per additional SVR in comparison to the previous standard of care (rather than within each regimen). We have modified the summary language in the final report to distinguish between findings for genotype 1, treatment-naïve patients and other subpopulations.*
8	Summary: Why were the multiple advantages of SOF+SMV x 12 weeks over SOF+RBV x 24 weeks in interferon-intolerant genotype 1 patients, as described throughout your document, not mentioned in the summary? SOF+SMV x 12 weeks is at least $90,000 less expensive on a cost per-cure basis than SOF+RBV x 24 weeks in genotype 1 patients, yet you note that many insurers do not cover it. For our patients who have the most urgent need for immediate treatment and cure, such as those with advanced, compensated cirrhosis, your report does them a disservice.	*We believe that the evidence on the potential advantages of SOF+SMV is tempered by limitations on currently-available data from COSMOS, such as no publicly-available data on performance in patients with advanced liver disease, the small sample size and lack of a control arm, and no peer-reviewed publication of trial results. These are noted in the report in Section 6.3.*
Paul J. Pockros, MD, Liver Disease Center, Scripps Clinic, La Jolla, CA		
1	Your conclusion that sofosbuvir is "low value" is clearly not based on data or science. There are a number of publications which demonstrate the cost of untreated hepatitis C and it exceeds the cost of treatment significantly, even at the cost of current regimens with SOF. As well, the QALY increment with SOF therapy is <50,000$/yr by any calculation used (Younossi Z, et al. J Hepatology Feb 2014). As a treating physician I can assure you that patients are no longer willing to fail first generation DAAs or PEG IFN and RBV before initiating treatment with SOF. Your conclusions are clearly based on inadequate or inaccurate information. Please reconsider.	*Thank you for your comments. We believe that our estimates of the costs of liver-related complications, cost reductions from achieving SVR, and cost of drug therapy are reasonable but have nevertheless tested their robustness against other estimates in the final report. With regard to the evaluation cited, results differ from our own primarily because (a) all-oral therapy was assumed to result in "cure" for 99% of patients, and (b) costs of all-oral therapy were assumed to be at most 50% higher than prior triple therapy. Drug acquisition costs for the current all-oral regimen available (SOF+SMV for 12 weeks) are 65-85% higher than those of prior triple therapy.*

Paul Justison, Oakland, CA		
1	If the national news networks stopped their coverage of a presidential election after 10 states had reported and the polls were open everywhere else, there would be a national outcry over their incompetence. But what we have in this study is something very similar. The main events - the last 40 states so to speak - have not yet come forward. I speak of the all oral combinations sponsored by Gilead and Abbvie, which will be approved within the year. These combinations have a wealth of data supporting them, very high SVR rates, shorter treatment, and very low A/Es. Had the study included these, the results would have been far different. For example on page 78, the study gives the cost of an additional SVR for Telaprevir treatment at $189,000. This is more than the cited cost of an additional SVR for Sofusbuvir/Simeprevir (Sof/Sim) treatment at $171,000. Since the about to be approved therapies are similar to Sof/Sim, they will also be more cost effective than the outmoded Telaprevir treatment.	*Thank you for your comments. While we recognize that there will be a need to produce multiple updates of this review as new therapies are approved by the FDA, CTAF has also recognized that patients, providers, payers, and other decision-makers need information now on the new therapies that are available. We note that AASLD/IDSA and the VA have adopted similar approaches for the development of "real-time" guidelines that will change as new therapies are approved.*
2	On page 59 the model assumes "patients would complete and be fully compliant with therapy." Since telaprevir therapy involves longer therapy, more rigorous dosing, and has far greater side effects than Sof/Sim and the new comparables, the assumption is biased. So is the assumption - "no differential costs assumed for identification and management of side effects and other drug related harms".	*As mentioned at the CTAF meeting and now highlighted in the final report, any measure of SVR already incorporates suboptimal compliance, as patients discontinuing treatment would be recorded as not having achieved SVR. While side effects were not explicitly incorporated into this model, rates of discontinuation from trials due to adverse events were presented, and the report highlights in several places the higher rates of discontinuation in the telaprevir and boceprevir trials.*
3	It should also be noted that costs for liver complications were taken from Florida Medicaid data. The report does not indicate what corrections were made to the Florida Medicaid data to make them relevant to California. Unless the data were corrected, it gives another bias against newer treatments.	*We are unclear how use of data from another jurisdiction introduces a "bias" against newer treatments. In addition, the analysis we used focuses on the "attributable" costs of advanced liver disease in comparison to a hepatitis C cohort without disease. While the costs incurred in any particular jurisdiction are likely to vary, the magnitude of incremental costs for liver disease is likely to be similar across jurisdictions.*
4	To estimate future costs of HCV, the report relies on projections of cirrhosis and liver complications over a 20 year period. There certainly are many academic studies estimating the impact over that period. It is, however, a	*The projections used were from a meta-analysis of studies examining rates of progression and disease in a newly-diagnosed (not newly-infected) cohort; the duration of disease varied in these studies. Nevertheless, our final report*

	graduate student error to use these estimates to project future treatment costs. HCV is a progressive disease and the vast majority of HCV patients have had the virus for 30, 40, or 50 years. To use 20-year historical data with a mid-point of year 2000, or earlier, to project costs for a future with a mid-point of say, year 2025, is to seriously underestimate the impact of disease progression and the costs of untreated HCV. Actual rates of cirrhosis, liver complications, and costs of untreated HCV could be double or more your estimates. (See chart on page 4.)	*includes estimates of future costs and cost offsets among patients at varying levels of liver disease, with incidence rates adjusted accordingly (for example, rates were assumed to be 4 times greater among patients with METAVIR 3-4 scores vs. METAVIR 0-2). While cost offsets naturally varied in absolute terms, these adjustments did not change the overall conclusions of our analyses.*
5	The report estimates the cost of treating Californians with HCV. But, it gives no time period for the costs, and without a time period it generates a very scary headline number of $32 billion. But what is this number based on? Treatment over 10 years? 5 years? There are only a limited number of Hepatologists and Gastroenterologists in California, and a reasonable projection of the costs of care in California, would be based on how many they could actually treat within a given timeframe. This report clearly did not do that.	*Please see our response to Dr. Saab (#4, on page 3 of this document) regarding the size of the treated population. We have also clarified in the final report that the budgetary impact was estimated over one year based on initial drug costs and then reduced according to estimated 5- and 20-year cost offsets.*
6	CTAF is rigorous in asking for conflicts of interest of others, and I agree, conflicts of interest should be clearly stated by all. Of course, this should include the health insurance industry itself. CTAF and its parent appear to be dominated by the health insurance industry. The facts about this relationship should be made clear and transparent, including that of panel members whose business models are dependent on links to the insurance industry. The curious role of UCSF should also be noted. The world class status of UCSF is unquestioned, but is, to put it politely, unseemly, when so many members of the same institution serve as judge, prosecutor, witness and jury in a matter of importance to the entire nation.	*While CTAF and ICER receive grant funding from governments and non-profit foundations, as well as unrestricted funds from insurers and manufacturers, the role of CTAF and ICER is to produce independent and objective evidence assessments. CTAF and ICER staff are free of all financial conflicts with both health insurers and manufacturers.* *Four of the 15 CTAF panel members are affiliated with UCSF, but all represent themselves on the panel, not their institution. Dr. Tice, Senior Medical Advisor to CTAF, is also affiliated with UCSF and is free of financial conflicts.*
Andrew Reynolds, Hepatitis C Education Manager, Project Inform, San Francisco, CA		
1	Within the birth cohort, with an HCV prevalence of between 3-4%, the impact of screening would be dramatic. Several studies have shown that by screening this population, over 800,000 previously unknown infections would be discovered, up to 121,000 deaths averted, and	*Thank you for your comments. Other than to note the potential for expanded screening efforts to increase the number of patients presenting for treatment, considerations regarding reduced disease transmission were outside the scope of this review, which was*

	up to 19,000 liver transplants averted (Rein 2012, McGarry 2012). People who inject drugs and other at risk account for most of the incidence of HCV, and screening and treatment of this population, in addition to averting deaths and preventing HCV-associated liver complications, has the additional benefit of preventing new infections.	*focused on the comparative effectiveness of new treatment options for hepatitis C.*
2	When voting on the clinical effectiveness and value of a simeprevir-based regimen versus a telaprevir-based one, a panelist remarked that since interferon was the cause of the severe side effects of both regimens, both PIs were essentially the same. In fact, a telaprevir based regimen is much more difficult to tolerate, as indicated by both the drug label, and several research studies presented at scientific conferences.	*Both the report and slides document the increased potential for side effects with first-generation protease inhibitors (PIs) beyond that attributable to interferon (for example, see Sections 1.3 and 6.9 of the report).*
3	[At] one point in the discussion, the moderator of the policy roundtable stated that the AASLD/IDSA Recommendations for Testing, Managing and Treating Hepatitis C recommended a combination of sofosbuvir and simeprevir as front line therapy, and he highlighted the high cost of this combination. In fact, the AASLD/IDSA Guidelines, recommend sofosbuvir + ribavirin + pegylated interferon as the first choice of HCV therapy. The group does recommend a combination of sofosbuvir + simeprevir with or without ribavirin for patients who are treatment naïve but who are ineligible to receive interferon, however, they note: "This regimen should be considered only in those patients who require immediate treatment, because it is anticipated that safer and more effective IFN-free regimens will be available by 2015 "	*The guidelines recommend SOF+SMV±R as the current treatment of choice for treatment-naïve genotype 1 patients who are ineligible for interferon, AND in all genotype 1 patients who have failed prior therapy (regardless of eligibility for interferon). We note that, while the qualifying language on reserving off-label combination therapy for those who need immediate treatment is mentioned in the treatment-naïve section of the guidelines, such language is not present in the section on nonresponders.*
4	Finally, its worth briefly discussing the most recent mortality data presented from the CHeCS Study, to highlight the importance of screening and treating HCV in a effort to avert deaths from this disease. Reena Mahajan and colleagues analyzed data from the CHeCS study and found that HCV was a significantly under-reported cause of death, and may in fact lead to approximately 80,000 deaths per year. The mortality rate for people with HCV is twelve times higher than the general population. The average life expectancy for people with HCV is 59 years of age, compared to 74 years of age for	*We have added text to the final report to note that hepatitis C is under-reported as a cause of death.*

	people without HCV. These numbers are significantly worse than what has been previously thought, leading the authors to conclude: "For purposes of public health, policy planning, disease modelling and medical care, this is a huge burden that should be reported and hopefully spur public health action as curative, all-oral therapies are becoming available to treat HCV" (11).	
Rachel McLean, Viral Hepatitis Prevention Coordinator/STD Healthcare Policy Analyst, California Department of Public Health, Sacramento, CA		
1	First, I would reiterate the points I made in my earlier comments and ask the report's authors to address the limitations of their methodology. Specifically, I think the outcomes would have been very different had the authors factored in the anticipated (and most likely shorter) life expectancies of persons who have had HCV for 30 years prior to diagnosis. Many people with HCV will die of all-cause mortality before ever being screened, diagnosed, or treated. Additionally, the model does not appear to account for the costs that will be borne by Medicare given the age range of prevalent cases. Also, it is not clear from the methodology at what point the HCV natural history "clock" was started—at the time of infection (like 30 years ago) or at the time of diagnosis (in the model, around age 60). This is important because it will affect the number/severity of liver complications expected in the theoretical patient cohort.	*Thank you for your comments. As noted at the meeting, any accounting for competing risks would have served to reduce rates and costs of downstream events for the hypothetical cohort (given attrition over time), but would NOT have materially impacted our estimates of the relative effects of any one treatment regimen vs. another, as there are no data to suggest that any one regimen has a differential effect on all-cause mortality vs. any other.* *We have clarified in the final report that the "clock" starts at the time of diagnosis (not infection) in our analyses.*
2	Regarding the natural history of HCV and the previous standard of care with boceprevir and telaprevir for genotype 1, I am not a clinician, but follow FDA label updates closely and send them to the members of the California Viral Hepatitis Clinical Task Force, which includes primary care providers and specialists. Both the labels for BOC and TLV have had numerous label updates to account for their considerable side effects and toxicities, and these considerations did not seem to be given sufficient weight in the panel's deliberations. One panelist suggested that the toxicity of PEG/RIBA plus BOC/TLV was due to the interferon. However, updated FDA labeling for both drugs contradicts this assertion.	*Please see our response to Mr. Reynolds (#2 on page 12). We believe that the side effects of first-generation PIs (above and beyond those of PR therapy alone) were documented in both the report and presentation of findings.*
3	Not discussed by the panel were the considerable extra-hepatic complications of chronic HCV infection, regardless of disease	*As stated in response #1 above, the focus of this review was on the comparative effectiveness of treatment regimens for hepatitis C, not on a*

	stage (Louie, 2012), which may have limiting effects on patients' quality of life and life expectancy. The panel also focused on symptoms, yet most people with chronic HCV have no symptoms, even while liver disease is actively progressing to advanced cirrhosis/fibrosis or hepatocellular carcinoma.	*complete documentation of the disease's natural history. While there are no data suggesting differential effects of treatment on extra-hepatic manifestations, we do note that our estimate of the annual costs of care for patients who do and do not achieve SVR includes costs both related and unrelated to hepatitis C.*
4	Third, I wanted to address the panel's question about the HCV reproduction ratio or R0 "(r-nought" or number of persons someone is likely to infect). I was only able to find papers estimating transmission patterns for injection drug users, which account for more than two-thirds of new HCV infections.	*Please see our response #1 to Mr. Reynolds on page 11.*
Craig Ennis, MD (affiliation unknown)		
1	I was recently informed of Blue Shield of CA decision to restrict use of sofosbuvir to cirrhosis pts only. I strongly disagree as this is the biggest breakthrough in the treatment of chronic viral treatments ever. You fail to realize this a 12 week treatment and curative in over 80% of cases. No HIV treatment is curative and all are lifelong with open ended costs that will exceed that of sofosbuvir. Restricting its use to cirrhotics only is very short-sighted. If we use this therapy we will prevent cirrhosis from occurring in many cases. Need I remind you how much you spend on one cirrhotics pt as they go through transplant with its attendant complications and long term expensive immunosuppressant therapies? Be advised, your decision to restrict the use of one of the greatest breakthroughs in viral treatment will not stop us from appealing repeatedly to you. It's in the best interests of every hep C pt that I do it. I already spent 2.5 hours on the phone convincing an out of state insurance to cover it in a 35 yo who now has undetectable viral load. Get ready, we are going to call every time if we have to in order to get use of this truly revolutionary life saving therapy.	*Thank you for your comments. The results of the CTAF meeting deliberation and votes do not represent a coverage decision.*
Christian B. Ramers, MD, MPH, Director, Graduate Medical Education – Assistant Medical Director, Family Health Centers of San Diego, San Diego, CA		
1	Treating and curing Hepatitis C has innumerable benefits, that are just beginning to be uncovered by an anemic national research agenda. Achieving a Sustained Virologic Response (SVR) results in a 90% reduction in liver disease, a 70%	*Thank you for your comments.*

	reduction in Hepatocellular Carcinoma, and a 50% reduction in all-cause mortality. There is evidence that treating Hep C actually improves neurocognitive functioning and can reverse pre-diabetes. There is likely to be a great deal more evidence on the basic science front regarding the chronic inflammation that subsides when Hep C is cured. There are thousands of babyboomers who are actually dying NOW of liver disease that could have been avoided if their Hep C was treated much earlier. The current battle over the price of Hep C treatments will go down just as the already-fought battle over HIV drug prices did. Eventually we will realize that it is absolutely INHUMANE to offer state-of-the-art curative treatment, with many benefits only to the wealthy, while the most affected populations suffer ongoing consequences. I urge the health officials, insurance executives, and pharmaceutical companies to work together to negotiate a solution that allows patients that need treatment to be treated. What we have currently is an inequitable, prejudiced, unfair system that systematically excludes the poor from accessing a potentially dramatic improvement in health status.	
Gregg Alton, Executive Vice President, Corporate and Medical Affairs; and Hans Reiser, MD, Senior Vice President, Medical Affairs, Gilead Sciences, Inc., Foster City, CA		
1	The CTAF report significantly underestimates the full lifetime costs of treating chronic HCV. In addition, the CTAF analysis unduly discounts the value of initiating treatment at early stages of disease, thus reducing the human and economic costs of cirrhosis, liver cancer, liver transplants and deaths from HCV. A 2011 Henry Ford Foundation study of patients with end-stage liver disease estimated their annual medical cost at $60,000.	*Thank you for your comments. The analysis described (Gordon, 2012) estimates the annual ATTRIBUTABLE cost of end-stage liver disease to be approximately $42,000 (the estimate provided in the comment does not account for costs of care among patients without liver disease, the appropriate referent category). Our final report includes an alternative analysis using the $42,000 estimate. Use of this cost estimate affected cost offsets to a moderate extent but did not affect the major findings of the base case analyses.*
2	The draft CTAF report concludes that for the majority of patients, the downstream medical cost benefit of treating most hepatitis C patients with sofosbuvir (SOF) is not outweighed by the upfront cost of treatment. Any cost offsets downstream of treatment with SOF (from fewer liver-related complications) would represent less than 10%-20% of upfront treatment expenditures after 5 years, and only recoup	

	about 66% of upfront treatment costs after 20 years. However, the report finds a stronger value proposition after 20 years for the use of SOF in patients with advanced liver fibrosis. These findings are in contrast to several recent publications supporting the cost-effectiveness of SOF-based regimens vs. other comparators. (Younossi ZM, et al. AASLD 2013. #368, Younossi ZM, et al. AASLD 2013. #369, Younossi ZM, et al. ISPOR EU 2013, Abstracts accepted to DDW and ISPOR 2014). When evaluated by ICER (incremental cost-effectiveness ratio) or the cost per SVR, SOF-based therapies were shown to be the most cost-effective treatment option for patients infected with HCV GT 1, including those who are difficult to treat (Table 1). These analyses were based on a decision-analytic model that projected health and economic outcomes for patients with chronic HCV infection treated with SOF-based regimens compared with currently available comparators. The state-transition model had six health states with annual transitions: without cirrhosis, compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), liver transplant and death.	*None of these evaluations appear to have been published in the peer-reviewed literature. In addition, the cost per SVR data presented in the Table appears to be an "intra-regimen" calculation. In keeping with standards for economic evaluation, the incremental levels of cost and SVR should be compared to a referent treatment regimen to allow for true calculation of cost-effectiveness (i.e., the expenditure required to achieve an additional SVR vs. referent treatment).*
3	Furthermore, initiation of HCV therapy at an earlier disease stage (i.e., in patients without cirrhosis, with METAVIR fibrosis scores F0-F3) yielded substantially fewer cases of CC, DCC, HCC, liver transplant, and HCV-related death, stemming from higher SVR rates among non-cirrhotic patients than cirrhotic patient. Consequently, the downstream total cost of care associated with advanced disease will be reduced substantially with earlier initiation of treatment. For patients infected with HCV genotype 1, cases of liver disease complications were threefold lower, and total costs of care were 38% to 46% lower when therapy was initiated at the non-cirrhotic stage than at the cirrhotic stage.	*In response to this and other comments, the final report includes alternative analyses that examine the effects in patients with milder levels of fibrosis (METAVIR F0-F2) vs. advanced fibrosis (METAVIR F3-F4). See response #4 to Mr. Justison on page 10.*
4	The most sensitive drivers in any HCV cost-effectiveness model are drug costs and SVR rates of the various regimens. The CTAF network analysis for SOF estimated an SVR of 83% among GT 1 treatment-naïve patients, whereas clinical studies with SOF showed SVR rates of 89-91%.	*Please see our response #4 to Dr. Graham on page 8.*

	Among GT 1 treatment-experienced patients, the CTAF model estimated an SVR rate of 67%; however, 71% is the estimated response rate based on analysis conducted by the FDA utilizing multiple baseline factors traditionally associated with lower response to interferon-based treatment that would predict the response rate in patients who previously failed pegylated interferon and ribavirin therapy (SOF US Prescribing Information).	*The SVR rate was adjusted for treatment-experienced patients to 71% for the CTAF presentation and is also reflected in the final report.*
5	To ensure consistency of the analysis, it is important to understand the details of how the patient populations were defined (ie. proportions of nulls/partials/relapsers in the treatment-experienced population). For example, 90% was quoted as simeprevir's SVR12 in treatment-experienced trials, which reflects the SVR in relapsers and not null or partial responders. The FDA analysis estimated an SVR rate of 51% for SMV + PegIGN + RBV for patients with the combination of IL28B non-CC alleles, HCV RNA >800,000 IU/mL and Metavir F3/F4 fibrosis.	*Please see our response #5 to Dr. Graham on page 8, noting the lack of subgroup data as specified in the comment for all relevant treatment regimens.*
	In addition, the draft CTAF report did not provide estimates of SVR rates for SOF in certain subpopulations vs. comparators (e.g., SOF in cirrhotic vs. non-cirrhotic or HIV/HCV co-infection) for GT 1 patients.	*The subgrouping that was performed (genotype, prior treatment status, interferon eligibility) was judged to be most important based on clinical expert input and was consistent with the stratification of recommendations in the AASLD/IDSA guidelines.*
6	The draft CTAF report utilized adverse event rates based on clinical trials, and reports of adverse events and discontinuations from real world studies were not mentioned.	*We chose to estimate adverse event rates from controlled studies as the most reliable estimate of the incremental effects of DAA agents over PR therapy alone.*
7	The CTAF model collapses all liver complications into one condition, regardless of severity, with an estimate of $25,728 per year based on a Florida Medicaid population (Menzin 2013). However, published costs of liver disease by severity show substantially higher costs in association with progression of liver disease (Gordon SC, et al. Hepatology 2012 and C McAdam-Marx et al. J Manag Care Pharm 2011).	*We are unclear where the estimates presented in the comment are derived from. Gordon and colleagues present the annual OVERALL costs (HCV-related and unrelated) as $59,172 for patients with end-stage liver disease vs. $17,037 for non-cirrhotic disease (Table 4 of the publication), yielding an attributable cost of approximately $42,000 per year. We used this cost estimate in alternative analyses for the final report, as noted in response #3 to Dr. Saab on page 3. In addition, as noted previously during the stakeholder conference call and the CTAF meeting, the McAdam-Marx analysis unfortunately compared costs of care for patient groups at varying levels of hepatitis C disease progression to comparator patients WITHOUT*

		hepatitis C, rather than to patients with hepatitis C but without hepatic complications.
8	The budget impact model includes the assumption that 50% of patients with HCV who are aware of their disease will be treated; however, the clinical capacity to manage the treatment all these patients may not be feasible. Therefore, the real costs of managing these patients may be lower.	*In response to these and other comments, we have added a budget impact scenario in which 25% of infected patients are treated.*
	In addition, the CTAF model does not take into account the increased costs of following HCV-positive patients compared to non-infected patients.	*All patients followed in the model were assumed to be infected with hepatitis C. The estimate derived from the Manos study was used to estimate the annual costs of care for patients who do and do not achieve SVR. Annual costs were approximately $4,000 higher in patients not achieving SVR. Note that this was estimated separately from the cost of liver-related complications.*
9	Patient perspective is not accounted for in the draft CTAF analysis. Therefore, it is important to consider the implications of patient-reported outcomes data on disability and adherence to treatment.	*We have consistently noted this as a limitation of our analysis.*
10	A public health implication to consider with HCV is that unlike other disease areas, HCV can be cured, so the benefits of treatment are nearly instantaneous instead of the need for lifelong therapy as seen with HIV. This gives an opportunity to eradicate HCV from the entire population.	*As noted in responses to Mr. Reynolds and Ms. Mclean, our intent was to assess the comparative effectiveness and comparative value of newer treatment options for hepatitis C, not to evaluate the impact of treatment on disease transmission or epidemic status.*
Richard K.P. Sun, MD, MPH, Chief, Clinical Programs, Policies, and Procedures Unit, Health Plan Administration Division, California Public Employees Retirement System, Sacramento, CA		
1	We at the California Public Employees' Retirement System (CalPERS) have been following the CTAF deliberations on hepatitis C treatments with some interest. Today I noticed that Figures 6 and 7 in the draft report posted on the Web were quite different from Figures 6 and 7 in the slides for the 3/10 meeting. See attached Word file. What happened? Were the draft report's Figures in error? If so, I would recommend that an Erratum be placed in the PDF file to prevent any possible confusion.	*Thank you for your comments. There was no error. Based on feedback received during our public stakeholder call on February 20th, we decided to change the format of these figures for the meeting presentation (the new format will also appear in the final report). The initial figures present the "cost offsets" at 5 and 20 years as negative numbers. The comment received suggested that we subtract the cost offsets from the total cost estimate assuming newer regimens are used (the "New Rx $" bar on the graph) and present all results as positive numbers instead.* *So, for example, in the initial Figure 6, the 20-*

		year cost offset for all genotypes was estimated to be approximately $13 billion. In the revised Figure 6, this offset has been applied to the incremental cost from switching to newer regimens, reducing that incremental cost from approximately $18 billion (the difference between the red and blue bars on the graph) to approximately $5 billion (the difference between the purple and blue bars on the graph). *The change in figure design has been made clear in the final report.*
Connie Chiang, PharmD, Associate Director, Medical Information, Janssen Scientific Affairs, LLC		
1	Consider including SVR rates for SMV+ PR without Q80K. Based on label and AASLD/IDSA Guideline recommendations for excluding patients with Q80K, using these SVR rates in patients with G1a without Q80K and G1b would impact the NMA and overall model results.	*Thank you for your comments. We revised the network meta-analysis to account for genotype 1a findings in patients without the Q80k polymorphism and have incorporated these findings into both the meeting presentation and final report.*
2	Incorporate durations of therapy for all patient types and all regimens into the model: • Naïve and Relapsers to PR: telaprevir+PR treatment is based on RGT and can have 24-week or 48-week dosing of PR. For example in the ADVANCE trial, 58% of the telaprevir treatment-naïve patients were eligible to receive 24 weeks of total treatment. For simeprevir+PR, all naïve and relapser patients including those with cirrhosis receive 24 weeks of PR therapy • Non-Responders (partial and null) to PR: for telaprevir+PR and simeprevir+PR, all patients receive 48 weeks of PR therapy • Cirrhotics: As noted in the telaprevir full prescribing information, patients with cirrhosis may benefit from 48 weeks of PR therapy including naïve and relapsers	*As noted in response #5 to Dr. Graham on page 8 and response #5 to Mr. Alton/Dr. Reiser on page 17, trial reports did not consistently provide subgroup data according to categories of response to prior treatment. We have also included alternative analyses to the final report that explore the impact of assuming a mix of 24- and 48-week PR therapy duration on total costs.*
3	Use of drug cost references from a single source and point in time	*We have clarified the sources of drug cost. We continued to assume a drug cost for telaprevir reflective of the time during which it was the standard of care.*
4	Evaluate model sensitivity to cost assumptions including choices of brand versus generic ribavirin costs	*We believe that wholesale acquisition costs and average wholesale prices represented a uniform starting point for price discussions, recognizing that price will vary substantially between payers. Regarding the use of generic vs. branded ribavirin prices, while we would expect*

		that this would change treatment costs in absolute terms, it would not materially affect relative costs between regimens (since all current FDA-approved regimens still require ribavirin).