Reviewer's report

Title: Cost-Effectiveness of Sofosbuvir-Based Treatments for Chronic Hepatitis C

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Reviewer: Sergio Iannazzo

Reviewer's report:

This is an interesting study, focused on a topic that deserves a lot of attention today: new treatments for Hepatitis C. A new breadth of treatments is becoming available in these days, and their effectiveness is in some cases impressive, but all of them are coming to market with important costs to be borne by National Healthcare Systems (in Europe) or by third-party payers (in the US). This is motivating the emphasis on health economic assessment in this field. The current study seems well conducted or at least in line with the current standard of modelling in this therapeutic area. One major limitation is however the lack of mention to treatments newer than Sofosbuvir, that have been approved by the FDA and included in the latest revision of the clinical guidelines for CHC in the US (AASLD). For this and other reasons detailed here below, I believe that this paper requires some revision before being considered for publication.

Major Compulsory Revisions

1. Abstract. The description of the comparators tested in the cost-effectiveness analysis is not clear in the abstract. Please list them out clearly. A sentences like “different treatment strategies” is too generic and does not inform the readers on what have been really studied in this analysis

2. Abstract, results section. Please describe (in the methods section, see previous comment) what is meant by “two-phase treatments”

3. Abstract row 11; Methods first paragraph. Can the authors explain why their analysis is limited to males only? Further on this point, what is the basis for the assumption of 45 years initial age of the simulated cohort? Is this based on the cohort characteristics in anyone of the mentioned RCTs of sofosbuvir? This would be acceptable but needs to be specified.

4. Background, third paragraph. The authors state that “Recently, sofosbuvir (brand name Sovaldi) as a new component of interferon-free oral regimen has been approved by the U.S. Food and Drug Administration (FDA) for treating CHC.” The approval of sovaldi dates back to December 2013. More than one year is quite a long time frame in this rapidly evolving therapeutic area. There is now an assortment of hepatitis C treatments. This includes Viekira Pak (ombitasvir, paritaprevir and ritonavir tablets co-packaged with dasabuvir tablets), Olysio (simeprevir) and Harvoni (ledipasvir and sofosbuvir), just to mention the latest approvals. The latest update of the clinical guideline by the AASLD (and other organizations) has already included all of them
In this context the current analysis presenting a comparison of Sovaldi with Peginterferon-ribavarin (P/R) appears to be out-dated. As a consequence the authors need to clarify what was driving the design of their analysis. Was this driven by the fact that, regardless the abundance of more effective treatments for CHR, P/R is still regarded as the standard of care? Or was this simply linked to the available clinical evidence of the effectiveness of sofosbuvir (i.e. availability of only the comparison with P/R from RCTs)? This should be discussed and explained in the introduction /aim and discussion sections (as a clear limitation of the analysis).

5. Methods, second paragraph. The authors declare that all costs were inflated to 2013 dollars. Please add the reference for the relevant price index that was used. Since we are today in 2015, I believe that a refresh of costs is needed. Please revise the costs in the analysis using the latest available price index (Q3 2014?).

6. Methods, Sensitivity analysis. The authors declare “In addition to one-way sensitivity analyses for all variables, we consider the effect of simultaneously changing all of the parameters values in the same direction.” This type of analysis is providing just a limited information on the overall stability of the model, because some parameters can have a positive impact of the ICER (for instance cost parameters) while others have a negative one (for instance the effectiveness of the studied drug). Thus while setting all parameters in the same direction their summed effect may elide one with the other. A standard approach to test the overall stability of a model is to perform a probabilistic sensitivity analysis, and to verify the reliability of base case results with cost-effectiveness acceptability curves. I recommend performing this analysis.

7. Table 7.1 and table 7.2 in Results section. The layout of these 2 tables should be improved to provide more clarity. More in detail the ICERs in the last column to the right are calculated with what comparators? Please also specify the criterion used (i.e. the threshold) to judge one alternative “inefficient”

8. Results, Sensitivity analysis. The section that reports the results of the one-way sensitivity is poorly detailed. Sentences like “little effect” or “certain parameters changes” are too generic. The entire section needs to be revised in order to provide more punctual information. I recommend including some sort of visual representation of the uncertainty, like for instance tornado diagrams. These can be included as appendixes.

9. The paper is missing a true discussion, to guide the interpretation of the results obtained in the context of similar studies published (for the US and/or other countries) and to discuss the limits of the analysis, with specific reference to the selection of comparators (see point 4)

Minor Essential Revisions

10. Abstract, row 5. Please specify that the price of $84,000 is applicable to the US. Alternatively add the setting of the cost-effectiveness analysis (i.e. the US) in the title.
11. **Abstract, row 11.** “Treatment-native” should read “treatment-naïve”. Please correct it throughout all the paper (the same spelling error is present in the main text in some instances)

12. **Methods second row of second paragraph.** If the analysis is limited just to males (this has, however, to be explained, see relevant comment among the major revisions) then “he/she” should read “he”

13. **Methods, Health-State Related Quality Adjusted Life Years.** The cited sources (i.e. 6, 20, 22, 23) for utilities appear to be previously published cost-effectiveness analysis, which, in turn, should have derived them by QoL studies. Please updated the reference, citing the original QoL study, or alternatively declare that your model is in line with previously published models

14. **Table 7.1** The number of the table and the legend is repeated identically for two subsequent tables. Please adjust the numbers and the legend.

15. **Conclusions, row 18.** Please correct spelling error “they did not significantly impacting

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests