Author's response to reviews

Title: Modelling the impact of improving screening and treatment of chronic hepatitis C virus infection on future hepatocellular carcinoma rates and liver-related mortality

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Author's response to reviews: see over
Dear Editors,

We would like to thank the reviewers for their comments regarding our manuscript and are happy to revise the article in line with these. Please find below a detailed point-by-point response to the comments:

**Major points**

1) *The introduction and results sections are well written, whereas Methodology section and Discussion sections need to be refined. In Methodology section, authors should consider adding more details about the model such as - how was the historical data extrapolated to make future assumptions, whether these involve patients listed for transplant/ transplanted, how were the costs calculated, if sensitivity analyses was done to identify uncertainties etc. Does this model assume that all the patients are treatment naïve?*

In line with the reviewer’s suggestion, we have added more detail to the methodology section. This includes information about how the model tracks chronic HCV infections, the basis for disease progression assumptions and the data used to validate inputs.

We have also discussed the sensitivity analyses in more detail in the methodology: ‘Sensitivity analyses and Monte Carlo simulations were performed using Crystal Ball, an Excel add-in by Oracle, to quantify the impact of uncertainties on modelled outcomes. Under Monte Carlo simulation, uncertain variables are represented as probability distributions and model outputs are recalculated 1,000 times to estimate a range of possible outcomes. Each recalculation uses a new randomly selected set of values from the input probability distributions and the likelihood of each outcome is recorded to generate 95% uncertainty intervals (95% UI). Beta-PERT distributions were used for all uncertain variables. Additionally, the impact of variations in the assumptions made in the ‘best case’ scenario (including the number of treated and newly diagnosed patients, and the segment of the population treated) on HCC cases and the number of liver-related deaths by 2020 was measured.’ The sensitivity analyses have also been discussed in more detail in the discussion section.

In response to the reviewer’s question: the model does not make a distinction between patients that are treatment naïve versus experienced. The following section has been added to the methodology for clarification: ‘The model does not distinguish previously treated
patients and naïve patients. However, average SVR rates used in the model encompass previously treated patients, naïve patients and patients treated at advanced stages of disease (F2-F4).’

We have also addressed this limitation in paragraph six of the discussion section.

In light of major point 7, we have removed the cost analysis from the study.

2) In Methodology, please clarify if the dataset used to derive ‘base-case’ scenario reflects mostly patients treated with ribavirin and peg-IFN or do these also include patients treated with protease inhibitors like boceprevir/ telaprevir which have been approved for more than 2 years or even newer medications like sofosbuvir etc. If yes, then what modifications were made to adjust for the different treatment modalities and their potential impact on future predictions? If the ‘base case’ involves only the patients treated with ribavirin and peg-IFN, then do you think the ‘base case’ reflects an outdated treatment regimen as opposed to the ‘current treatment strategies’?

We can confirm that the ‘base-case’ scenario does take into consideration patients treated with the protease inhibitors boceprevir and telaprevir. This has now been amended in the methodology and discussion. As discussed in the paper, the impact of newer therapies (which would include sofosbuvir) with improved SVRs are included in the ‘best-case’ scenario.

3) Was the model tested to back calculate the expected prevalence of Hepatitis C, including the development of HCC or decompensated liver disease, mortality using the historical data and then compared with the actual data to see if the predictions are close to the actual data? Is it possible to do this testing?

The model was validated using data from the Office for National Statistics (ONS) and Public Health England (PHE) [1-3]. From 1998 – 2012, the model trends well with PHE reported hospital admission data for end stage liver disease (ESLD) and hepatocellular carcinoma (HCC), but provides a more conservative estimate of cases for each [3].

References

4) In Methodology, under “Increasing diagnosis and treatment of HCV”, the model assumed that the number of patients treated increased from 5,430 in 2013 to 8,150 in 2014 and then to 11,710 in 2018. What was the basis of this assumption?

The increase in the number of treated patients was not an assumption per se, but an input necessary to achieve the optimal impact of new therapies on the HCV-related disease burden. We have now re-worded the methodology to ensure this is now clear: ‘To estimate the ‘best case’ of producing an optimal impact with new therapies on the burden of disease, increases in the number of treated patients were required. For the purposes of this analysis, the number of patients treated was modelled to increase from 5,430 in 2013 to 8,150 in 2014. The number of patients treated then increased to 10,190 in 2016, and 11,710 in 2018 (Table 2).’

5) In Results Section, Please include the respective data for historical cohort for HCV related morbidity and mortality in Table 3 for easier readability and comparison.

Rather than including historical data in Table 2, the historical data for 2013 has now been moved to Table 3. This, as the peer-reviewer notes, improves the readability for the base-case outcomes.

6) While it is certainly plausible and very likely that with Hepatitis C eradication, the rate of progression of liver disease will perhaps be slower. However, data is scant for patients who had already developed advanced fibrosis or cirrhosis and then undergo HCV treatment. In addition, it is not entirely known how HCV treatment changes the risk of HCC development in an already cirrhotic patient. This should perhaps be discussed in the Discussion/ Limitation section or an appropriate reference should be included that made the basis for calculation of reduction of HCV related morbidity/mortality in ‘best case’ strategy.

The following section has been added to the discussion in response to the above point:
'This analysis focused on chronically infected individuals. Once a patient achieved SVR they were removed from the infected cohort. Although studies have shown that patients with SVR retain some risk of HCC, decompensation and liver-related death, the rate of progression is substantially lower than in patients with current infection [1]. Additionally, because patients achieving SVR are not tracked, all re-infections in the model are handled as naïve cases. Combined, these two limitations suggest that the model may overestimate the impact that SVR has on HCV liver-related morbidity and mortality. However, any overestimate is likely to be limited. Firstly, the modelled scenario aims to cure patients before they progress to advanced stage disease, thus lowering the risk of disease progression after cure. Secondly, the risk of HCV re-infection is estimated to be small even in IDUs.' [2].


7) **The authors very cursorily address the cost effectiveness with the new strategy.**

*Further details should be given regarding the methodology behind cost estimations? If the primary aim is to see if the new treatments will be cost effective, then a detailed analysis should be included in the results including the current healthcare costs, main factors responsible for the cost including cost of treatment of HCV, cirrhosis related complications or HCV in addition to projected costs with base case strategy.*

We agree with the reviewer that if the primary aim of the study was to investigate cost-effectiveness, then a more detailed analysis of healthcare costs would be required.

However, the aim of the study was not to be a cost-effectiveness study, but rather to focus on minimising the burden of HCV disease progression. On this basis we have removed the cost analysis from the paper.
8) This section of Discussion on overcoming barriers to care can be curtailed as it does not add significantly to the strengths/ findings of the study. Neither is this the main focus or aim of the study and goes beyond the scope of data presented. Authors should consider condensing the last 2 paragraphs in the Discussion section. In addition, since the analyses for cost effectiveness is incomplete without adjusting for the treatment costs, as the authors have correctly identified, discussion regarding cost effective strategies for reducing HCV-related morbidity and mortality should be curtailed.

We agree with the reviewer that the discussion of barriers can be reduced as it is not the main focus of the study. Similarly, we are in agreement that the discussion of cost effective strategies is not necessary – especially as we have now removed that cost analysis from the study. On this basis we have removed the two paragraphs in question from the discussion section.

Minor points

1) There is data that genotype 3 incidence is rising in UK and genotype 1 is declining. Do you anticipate any major changes to your analysis based upon that or do you anticipate that there won’t be any significant changes? (Ref: Costella, Annastella and Health Protection Agency United Kingdom. Hepatitis C in the UK 2008. The Health Protection Agency Annual Report. Health Protection Agency Centre for Infections, London, 2008).

This is an interesting point raised by the reviewer. However, the HPA report provided by the reviewer states that ‘the proportion of genotype 3 infections has increased from 42 per cent in 2002 to 47 per cent in 2007 whereas genotype 1 infections have decreased slightly from 45 per cent in 2002 to 42 per cent in 2007.’ The genotype distribution used for our analysis was obtained from a more recent HPA report from 2011 [1].

The distribution reported in 2010 was 47% for genotype 3 and 44% for genotype 1. Therefore, it seems that the proportion of genotype 1 infections may have changed little in England between 2002 and 2010 (45% versus 44%). Furthermore, an increase in genotype 3 incidence was not reported between 2007 and 2010. Therefore, it is possible any potential increase in the proportion of genotype 3 infections has levelled out. Because of this uncertainty, we have felt it unnecessary to discuss the impact of increasing genotype 3 incidence versus declining genotype 1 incidence.
2) "The model estimates that 5,430 HCV patients were treated in England during 2010, based on the number of standard units of peg-IFN sold (IMS Health Incorporated; Danbury, Connecticut). Does this reliably capture nationwide peg-IFN sale?"

The modelled estimate of treated patients in England is in line with Public Health England estimates. The methodology has been updated to reflect this:

‘The model estimates that 5,430 HCV patients were treated in England during 2010. This was based on the number of standard units of peg-IFN sold between 2006 and 2011, with an estimated 26,670 patients treated in this period (IMS Health Incorporated; Danbury, Connecticut). This estimate is in line with those of PHE, which estimates that a total of 27,500 patients were treated between 2006 and 2011’.

3) Page 13, Line 353, 2013 and 49,730 need to be separated.

This has now been amended in the manuscript.

We would again like to thank the reviewers for their comments. We feel confident that we have now addressed the comments in sufficient detail and look forward to hearing from you soon.

Yours Faithfully,

Steve Ryder