**EUnetHTA JA2 WP5 – STRAND A**
**Public Consultation: Comments and Author's replies on the Draft Project Plan on 'Rapid Relative Effectiveness Assessment of new pharmaceuticals for the treatment of chronic hepatitis C'**

The Draft Project Plan on WP5-SA6 '**Rapid Relative Effectiveness Assessment of new pharmaceuticals for the treatment of chronic hepatitis C'** was open to public consultation between June 23, 2015 and July 7, 2015.

The aim of the Project Plan is to provide an overview on the planned processes, the scope, the scientific methods and the time-schedule for compiling a Pilot Rapid Assessment on the technology mentioned above. The Pilot Rapid Assessment (partly or as a whole) will be translated into national/local reports by participating WP5 members.

**Comments were received from:**

| **Institution** |
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| AIFA |
| ASSR, Emilia-Romagna region, Italy |
| AETSA |
| Department of Epidemiology, Regional Health Service, Lazio, Rome (referred to as Lazio) |
| The Norwegian Knowledge Centre for the Health Services (NOKC) |
| Bristol-Myers Squibb |
| Irish Haemophilia Society (referred to as IHS) |
| ELPA (European Liver Patient Association) |
| Ministry for Energy and Health, Malta (referred to as MoH Malta) |
| Janssen Pharmaceutical (referred to as JnJ) |

*01/09/2015*

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| **Institution** |
|---|
| MSD Europe Inc. |
| Scottish Medicines Consortium (SMC) |
| IQWiG |
| Agency for Health Technology Assessment and Tariff System (AOTMiT) Poland |
| NHS Latvia |
| Dutch National Health Care Institute (ZIN) |
| EFPIA |
| Regional Health Service, ESTAR, Firenze, Italy |

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**Summarized comments and replies:**

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| 1 | General | | ESTAR | The point that I offer to your attention is a methodological one and, in particular, focuses on the choice of the statistical models to be employed in the various meta-analyses.<br><br>Briefly, the vast majority of currently used models can be classified as follows:<br><br>1. Traditional models of frequentist meta-analysis (which were recognized to be a sort of worldwide "standard" until a few years ago); these may include **non-Bayesian** models of network meta-analysis.<br><br>2. Models of Bayesian meta-analysis, the design of which generally conforms to a network of direct and indirect comparisons.<br><br>There is a plentiful literature in support of the two points described above. If requested, I am willing to offer a selection of the most authoritative studies and recommendations<br><br>Anyhow, the index term "Bayesian meta- | As stated, for NMA, preference will be given to Bayesian hierarchical modeling using Gibbs sampling. For some outcomes, Bayesian methods are not well developed yet, e.g. for survival data, other methods may be more suitable, but this is unlikely to be relevant in this project, that mostly deals with proportions.<br><br>For meta-analysis that are not network meta-analysis, we will use traditional methods, as they are more transparent and the techniques are more mature, validated and developed, meaning that there is much more experience in the use of these techniques and that the limitations are much better known<br><br>NMA is fairly experimental and controversial. We avoid the use of analysis methods that are too immature and where the validity of the underlying assumptions are not always well understood nor tested. |

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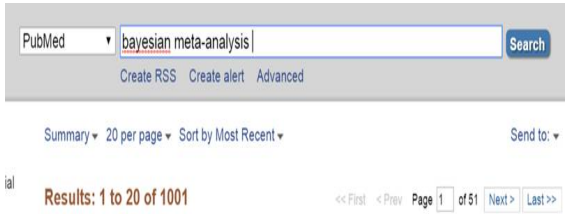
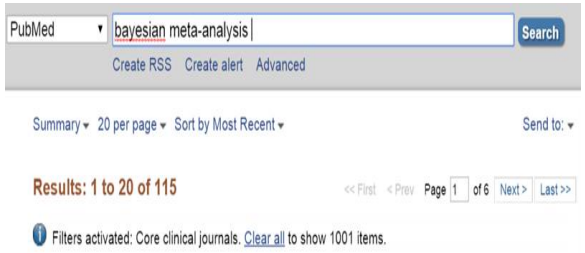
| | | | | analysis", for example, selects a total of 1,001 citations from PubMed (see below).<br>  <br><br>Likewise, the same search combined with the criterion of "Core clinical journals" selects 115 studies.<br>  <br><br>More importantly, if one gives a look at the meta-analyses published in 2014 -2015 in the top | |

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| | | | | journals (e.g. Lancet, Annals of Internal Medicine, JAMA, BMJ, Gastroenterology), it is really impressive to see that the Bayesian approach was employed in nearly 100% of cases.<br><br>In summary, my recommendations concerning the statistical model adopted for the meta-analysis are essentially the following three :<br><br>1. Avoiding the use of frequentist models of network meta-analysis (that are instead recommended in the current version of the protocol); the Bayesian approach (see Table 4) is mentioned as a model suitable for the analysis, but the details on the point are insufficient to understand how the analysis would be carried out. See the following document released by NICE that contains the necessary details: : Jonas DE, Wilkins TM, Bangdiwala S, et al. Findings of Bayesian Mixed Treatment Comparison Meta-Analyses: Comparison and Exploration Using Real-World Trial Data and Simulation [Internet].j Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 Feb. http://www.ncbi.nlm.nih.gov/books/NBK1 | |

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| | | | | 26104/<br><br>2. Adopting instead models of Bayesian meta-analysis. The main implication is that, consequently, the analysis will likely be focused not only on direct comparisons, but also on indirect ones. This feature is of interest because, in this way, a comprehensive summary of the available literature is generated on the basis of a single model.<br><br>3. Take advantage of some specialized functions of the Bayesian approach (for example, the capability to include some trials that are not interconnected within the meta-analytic network geometry and, consequently, would be left out in a traditional meta-analysis) | |
| 2 | General | | EFPIA | EFPIA notes the project initiated by EUnetHTA on "Rapid Relative Effectiveness Assessment of new pharmaceuticals for the treatment of chronic hepatitis C". **EFPIA considers that this project does not fit the purpose of EUnetHTA pilots of rapid assessment nor the objective of article 15 of the Directive on Patients' Rights in Cross-Border Healthcare (Directive 2011/24/EU)**. | The objectives of WP5 Strand A within the work of JA2 include:<br><br>❖ To test the capacity of national HTA bodies to produce structured core HTA information (full core/rapid HTAs) together and apply it in national context<br>❖ To implement, pilot and further develop models and tools as well as production processes to support collaborative |

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| | Scope of the pilot | | | EFPIA considers that the analysis envisaged by EUnetHTA is <u>not</u> a rapid assessment, contrary to what is suggested by the title of the project plan. **A rapid assessment is a rapid review of evidence available at launch submitted by the manufacturer (mostly relative efficacy evidence) in order to develop recommendations to support access decisions**. A rapid assessment is conducted at launch by authorities which have a role in access pathways, in order to support efficient, fast and high quality provision of evidence. To the contrary, the foreseen pilot reviews products that have already passed through most of the pricing and reimbursement processes nationally throughout the EU and does not directly involve the manufacturer. **EFPIA considers that pilots should focus on what a sustainable mechanism is likely to be able to deliver in the future, i.e. European assessments of relative efficacy at time of launch as a first data input into national HTAs.** Because of its scope, its timing, and its lack of engagement, EFPIA considers that this pilot is not a relevant exercise within Joint Action 2. | production of core HTA information with reinforced secretariat and coordination function<br>❖ To develop and test a methodological basis for European cooperation on HTA including guidelines for distinct methodological issues and quality improvement of evidence generation for HTA.<br><br>Our work is pioneering, and is designed with the aims of producing timely and transparent information of use by the members. Our remit is not limited to single technology appraisals. In the first five pilots, as WP5 has developed and explored joint HTA, we focused on single technologies, but were not limited to this in any explicit statement. Our work aims to support cross border health care by facilitating knowledge sharing and timely access to knowledge.<br><br>EUnetHTA was asked by DG SANTE to provide an overview of national HTA assessments of sofosbuvir. EUnetHTA conducted a review and found that many countries, especially smaller countries or those with less developed HTA processes have struggled to handle these assessments. |

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| | | | | | Therefore, a multiple technology appraisal, based on this needs assessment, is seen as both facilitating knowledge transfer, and providing information which can help members in their own assessments and decisions. Furthermore, based on a survey of 28 countries, by September 2014, 11 countries had not yet started an assessment of sofosbuvir. It is not the case that all countries have assessed or reached reimbursement decisions on all the compounds, and many countries have not had the resources to compare the compounds, as they received market access in short succession. Therefore, this assessment is both relevant and has a role to play in fulfilling a need for HTA information among the member states. We therefore consider this work not only highly relevant, but directly in line with the objective of Article 15 of the Directive on Patients' Rights in Cross-Border Healthcare (Directive 2011/24/EU), particularly with regards to item C of the objectives of the health technology assessment network:<br><br>(c) support the analysis of the nature and type of information that can be exchanged; |
| 3 | General | | EFPIA | Whilst EFPIA questions the general purpose of the pilot, EFPIA makes some general comments on some of the aspects raised by the project plan in case EUnetHTA decides to pursue this | EUnetHTA will pursue this project and thanks EFPIA for their efforts and comments submitted. |

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| | | | | project. | |
| 4 | General | | IQWIG | The document and the planned research question and methodology are in parts difficult to understand. This might partly be due to the structure of the document and the chosen presentation according to the project plan template (please see below). In addition to methodological comments, therefore, we are also providing suggestions which we hope could clarify ambiguities. In general, we would like to suggest that outside the current pilot, the structure of the project plan is discussed to support a clear presentation of the planned scope and methods. | The document follows the template structure of the project plan for all WP5 Strand A REAs. However it is correct that the other REAs conducted as part of WP5 have been on single technologies and the project plan template has been designed with this in mind. We will take this comment into consideration for improvement of the project plan and the project plan will be updated based on the received input of the public consultation. A final version is expected to be published in Q3 2015. It will also be taken into consideration as preparation for Joint Action 3. |
| 5 | General | | IQWIG | Please include (printable) page numbers in the document. The page numbers listed in the page number column of this document are referring to the electronic page number of the pdf-document. | Page numbers have been included in the document. |
| 6 | General | | SMC | There is some evidence in the UK that clinicians will prescribe some treatment strategies for a shorter treatment duration than which is licensed; will this be considered in the REA? | It has been decided to follow the indications, dosages and durations of treatment as are described in the EPAR by EMA. Therefore the local 'off-label' changes cannot be taken into account in this assessment, unless there is published high level evidence supporting the use in clinical practice. |

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| 7 | General | | MSD | Suggest evaluation of duration of therapy based on presence or absence of cirrhosis | As far as the data are available, we agree to include these subgroups. Please see the list of planned subgroup analyses. |
| 8 | General | | MSD | Suggest evaluation of duration of therapy based on patients being treatment naïve or treatment experienced | Please see the answer above. |
| 9 | General | | MSD | Suggest evaluating impact of drug with and without Ribavirin and its impact on efficacy. | Please see the answer above. |
| 10 | General | | MSD | Suggest evaluating impact of drug with and without Ribavirin and its impact on safety. | Please see the answer above. |
| 11 | General | | MSD | Report presence of baseline RAVs to the different HCV drug classes | Please see the answer above. |
| 12 | General | | MSD | Suggest Evaluation of drug in sub-groups of patients with high unmet needs (DAA failures), specific comorbidities that currently impose limitations for treatment (chronic kidney disease, inherited blood disorders) and high risk behaviors (Opioid substitution therapy) that impact HCV. | Thank you for the suggestion; this will be covered by specific trials or subgroup analyses. |
| 13 | General | | MSD | Consider evaluating drug-drug interactions with co-administered medications such as HIV antiretroviral therapy | This topic will be covered in safety analyses if resulting in AEs. The background science is covered in the EPAR. |

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| 14 | General, 19 | General and 5.1 | JnJ | **Milestones and Deliverables**<br><br>We would like to reiterate that we find it frustrating that stakeholders have been asked to submit evidence to a EUnetHTA pilot again without having time to digest the scope or remit of the review. For the record, our submission was expected on 29th May, yet the project plan defining the question to be addressed was only released for consultation, (so potentially not final) on the 23rd June. This expectation that stakeholders work 'blind' to the details of the question in hand continues to be a major source of concern, and if not addressed in the future, will likely undermine the credibility and sustainability of the platform. | This joint multiple technology appraisal is the first of its kind, and has called for novel processes outside the standard processes employed by WP5 Strand A.<br><br>Within the standard process of WP5 Strand A, for single technologies, MAHs prepare a first draft of the submission file without first having a project plan. This is clearly demonstrated within the WP5 Strand A procedure manual. MAHs receive an information package which includes a submission file template to guide work. A project plan is normally developed after the scoping meeting, which occurs following receipt of a draft submission from the MAH. So it is not a given that MAHs prepare submissions with a project plan already in hand.<br><br>However, we acknowledge this specific comment and this will be seriously taken into account in possible other rapid non-single technology assessments of a similar nature. We think that there are some considerations that led to the current organization of this pilot:<br><br>❖ The high level of need for this assessment based on the research conducted by EUnetHTA on national assessments of sofosbuvir as well as |

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| | | | | | interest by the European Commission and the member states, it was pertinent to conduct this assessment before the end of JA2<br><br>❖ Due to the time restraints WP5 had to develop a working model that was both timely and provided, as much as possible, opportunities for the input of stakeholders during the process. Stakeholder input is important and valued. WP5 involved the MAH at three different stages to provide input: at the start, at the consultation of the project plan and at the consultation of the draft assessment report.<br><br>As this is the first assessment of its kind within JA2 WP5, the procedures are novel and will be reviewed for future joint pharmaceutical assessments involving multiple compounds and marketing authorization holders. The input of stakeholders is important to us and will be taken into consideration as we move forward with further developing the procedures of joint assessment and cross border HTA. |
| 15 | General | | BMS | EUnetHTA REA should be voluntary. This project does not meet that expectation. | A company may choose to participate in a EUnetHTA REA and provide a submission file and collaborate with the coordination team as an |

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| | | | | | assessment is produced. However, it has been clearly defined within the working documents of EUnetHTA WP5 (including the information package sent to all prospective MAHs), that a decision by a MAH to not participate or provide a submission file does not automatically mean that an assessment will not go ahead. It has been clearly stated that in such a case, EUnetHTA WP5 may choose to continue an assessment based on publically available information when an assessment is deemed important and relevant to the member states. Such was the case with this assessment. |
| 16 | General | | BMS | Assessment should be based on manufacturers' submission including not only EPAR data but also the best available, robust indirect comparisons that use patient level data such as matching-adjusted indirect comparisons. | Ideally, such an assessment would include manufacturer's submissions. It has always been stated in EUnetHTA WP5 that this is the ideal manner of working. However, in cases of high need and relevance, it has also been clearly stated that an assessment may still go forward in the absence of a manufacturer's submission. In the case of this assessment, all MAHs were provided the opportunity to submit information (albeit within a shorter time frame than ideal). Furthermore, given that all compounds had received market authorization, the availability of public information was considered sufficient.<br><br>We cannot take for granted that patient level data such as matching-adjusted indirect |

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| | | | | | comparisons are robust - those techniques are new, rely on analyses that are experimental at best, are easy to manipulate, and the validity, especially the degree to which confounding is really addressed is difficult to evaluate. Therefore, these analyses are controversial. This position on this kind of analyses is shared by several HTA bodies, including NICE.<br><br>An individual based indirect comparison could be very useful, but on the condition that this is done by an independent organization, based on individual data of all treatments that are compared, and even then it is not clear if all important confounders are identified and measured with sufficient precision and validity. Such an exercise is far beyond the means of this project, as it requires not only access to the data but also a robust data management system to ensure protection of privacy, and a pre-agreed and validated method to do such an analysis |
| 17 | General | | BMS | Assessment should be timely. REA should be conducted early enough to help decision makers make fast access decisions. The timing of this REA comes when most new technologies have already passed through the pricing and reimbursement process nationally in the EU. | EUnetHTA WP5 agrees that an assessment should be timely. An assessment should also facilitate members by providing useful, transparent and transferable information. Based on the assessment of national HTA processes conducted by EUnetHTA WP5 at the request of the member states and the EC, not all countries had conducted assessments nor made |

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| | | | | | reimbursement decisions about all the compounds as of September 2014. Furthermore, the speed at which the new compounds hit the market meant that many countries did not have a chance to conduct comparisons of the compounds. Therefore, a comparison of these compounds has potentially a very relevant and useful place in national decision making processes when considering patient needs. |
| 18 | General | | BMS | The analysis envisaged by EUnetHTA does not meet the usual criteria for a rapid assessment. A rapid assessment is a rapid review of evidence available at launch submitted by the manufacturer (mostly relative efficacy evidence) in order to develop recommendations to support access decisions. A rapid assessment is conducted at launch by authorities which have a role in access pathways, in order to support efficient, fast and high quality provision of evidence. This pilot reviews products that have already passed through most of the pricing and reimbursement processes nationally throughout the EU. We consider that pilots should focus on what a sustainable mechanism is likely to be able to deliver in the future, i.e. European assessments of relative efficacy at time of launch as a first data input into national HTA. | It is not explicitly stated within the remit of WP5 that only single technologies may be assessed. Nor is it clearly stated that an assessment can only occur immediately following Market Authorization (as in the case of the first pilot, Zostavax). Further, as in the case of the sorafenib pilot, compounds may be assessed when reimbursement decisions have been reached in a number of countries. While it is ideal to conduct assessments on products where reimbursement decisions have yet to be made, this is a pilot process and thus this is not the only criteria for selecting a pilot within JA2 as we also focus on developing processes and methodology.<br><br>As the current situation of Europe is one in which the MAH largely sets the pace for submissions, and may submit requests for reimbursement at different time points, it is often the case that |

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| | | | | | there is variation within Europe on rate of submissions and subsequently the reimbursement decisions.<br><br>We do agree that an aim of WP5 is to develop sustainable mechanism for a model of cross border collaboration in HTA. However, in order to do so, joint assessments will need to take into account relevant issues for members and manners in which to deliver support through the exchange of information. It would not be correct to consider that every joint HTA produced will be relevant for all countries at all time points, Certainly not while there continues to be variation among the rates of submission and decisions around Europe. Rather, a sustainable system should include joint work that is maximally relevant to as many members as possible. |
| 19 | General | | BMS | The proposed methodology focuses on short-term outcomes and therefore may underestimate the long term clinical benefit of the technology such as avoidance of progressive liver disease, hepatocellular carcinoma, and liver transplantation. | Long term outcomes will be included if already available. Furthermore, individual countries will develop a health economic model including long term outcomes. |
| 20 | General | | NOKC | Please check that abbreviations are written in full the first time they are in use | The document has been checked and abbreviations will be explained when first |

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| | | | | | mentioned. |
| 21 | General | | AETSA | The number of the pages is not included. | Page numbers have been included. |
| 22 | Involvement of manufacturers | | EFPIA | EFPIA notes that EUnetHTA has contacted relevant manufacturers before initiating the pilot, but that manufacturers are not directly involved; EFPIA regrets that EUnetHTA chose to conduct a unilateral assessment without involvement of manufacturers. We call on EUnetHTA to also liaise with manufacturers of comparator products foreseen in the analysis. | Within WP5 Strand A, Manufacturers are invited to provide a draft submission file, attend a scoping meeting, and submit a final submission file. During the assessment phase, MAHs are invited to provide a round of comments after the editorial draft is completed, at the same time as the WP5 member consultation. This is the process of MAH involvement during the first 5 pilots.<br><br>As this pilot was unique in the work of WP5 Strand A, variations in the processes occurred for several reasons:<br><br>Multiple Technologies: A high level of interest and need was identified through requests by DG SANTE to EUnetHTA to provide an overview of national HTA assessments of sofosbuvir, as well as input from our partners. It was identified that multiple compounds for the treatment of Hep C were considered relevant to assess. Consequently it was deemed relevant to conduct a multiple assessment and comparison of the treatments<br><br>Multiple MAHs: As a result of so many |

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| | | | | | compounds under assessment, more than one MAH had to be involved in this assessment, which posed significant logistical challenges, such as completion of the submission file.<br><br>The timelines: owing to the need and relevance of this multiple technology assessment, it was important to conduct this assessment prior to the end of JA2. This resulted in very short timelines for such a large assessment<br><br>While WP5 would ideally have held scoping meetings as well as accepted draft submission files from multiple MAHs, this was simply not feasible given the time constraints.<br><br>Nevertheless, the feedback of stakeholders is important to EUnetHTA WP5 and to ensure stakeholder input could be accommodated despite such logistical constraints, an invitation was sent to all MAHs of the new hepatitis-C treatments to provide input in the form of additional data, as well as two consultation rounds, that of the project plan and a 2nd round which will occur during the assessment phase. This mirrors the MAH consultation in the previous 5 pilots.<br><br>It is interesting that EFPIA also proposes to contact the MAH of the comparator 'old' |

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| | | | | | treatments. That would be quite different from the approach that we had until now in the first five pilots and would seriously affect the timeliness of these assessments. Moreover, that might mean that we may also involve manufacturers of generic products if there products are relevant comparators. This could make the process even more complicated. |
| 23 | Health Problem Section | | MSD | Document importance of treating patients with specific co morbidities that currently impose limitations for treatment (chronic kidney disease, inherited blood disorders) and high risk behaviors (Opioid substitution therapy) that impact HCV | This topic will be covered by specific trials or subgroup analyses. |
| 24 | Minor Points | | ESTAR | 1. The Bayesian approach has ALREADY been applied to the assessment of treatments for hepatitis C, and also for hepatitis B. The two references are the following:<br>[1] Trippoli S, Fadda V, Maratea D, Messori A. Bayesian network meta-analysis to evaluate interferon-free treatments in naïve patients with genotype 1 HCV infection. Eur J Gastroenterol Hepatol 2015 Aug;27(8):983-984<br>http://www.osservatorioinnovazione.net/ | Thank you for the references. |

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| | | | | papers/ejgh2015.pdf<br><br>[2] Golan L, Wu Oa, Xin Ya, Sharon J. Hutchinsonb SJ, Neil Hawking H. Comparative effectiveness of antiviral treatment for hepatitis B: a systematic review and Bayesian network meta-analysis. Eur J Gastroenterol Hepatol 2015 (in press). ). Both papers are provided as a PDF attachment because these studies are very recent and do not yet appear in PubMed.<br><br>2. Another model of Bayesian statistics has been proposed for use in the real-world; the model is aimed at comparing the true effectiveness with that expected according to clinical trials. Refefence: Messori A, Brunetto MR, De Luca A, Zignego AL. Direct antiviral agents for treatment-naïve patients with genotype1 hepatitis C: statistical model for comparing outcomes between real world and clinical trials. Digestive Liver Disease 2015 (in press), available at www.osservatorioinnovazione.net/pap | |

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| | | | | ers/dld-2015-bayes.pdf<br><br>3. The Italian society of clinical pharmacy and therapeutics (SIFACT) has recently released a document with reasoned selection of the most relevant literature; the document is divided according to the main of current interest<br><br>(see http://www.sifact.it/sifact-bibliografia-epatite.pdf ) | |
| 25 | 4 | Section 1.0 | AOTMiT | AOTMiT is not involved in the assessment however we are substantially interested in the results and are ready to provide Polish data and to comment on the REA. All drugs in the REA has been assessed in AOTMiT on the base of applicant HTA analysis (verification analysis preformed) and some included on reimbursement lists (detailed info attached in separate file). | Thank you for this offer. |
| 26 | 4 | Project Plan | MoH Malta | Since there are 12 agencies who have a role as dedicated reviewer, is it possible that the review work for the dedicated reviewers is distributed (as has been done for the authors) in order to avoid duplication in processing comments by the authors due to similar comments? It will probabaly target the document's review more | This is a very valuable comment and the coordination team will try to find the most effective way for all parties involved to review the assessment. |

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| | | | | effectively and efficiently. | |
| 27 | 4;22 | Section 1.0, Section 10 | Lazio | Conflict of interest. The role and responsibilities of each project participant (especially those acting as author/co-author) in the pricing and reimbursement decisions at National level should be fully disclosed and should be also part of the conflict of interests statement/evaluation. | The roles and responsibilities of project participants are not part of the EUnetHTA Conflict of Interest policy (DOICU). We collect general information through the DOICU (question 1a) but it does not specify if someone plays a role in pricing and reimbursement, and we do not publish it. This is not a part of the current discussions and therefore this policy will not likely change in the near future.<br><br>We do not exclude assessors from joint assessments because they are involved in this work on the national level. This is not seen as a Conflict of Interest which is equal to conflict due to receiving payments or other material rewards from industry for instance.<br><br>We will not be including the information or the roles and responsibilities of project participants in the pricing and reimbursement decisions at National level in the COI statements. |
| 28 | 4 | Table 1 | AIFA | Since ethical, organizational and social domains will be addressed, please specify which institutions will be the authors of these domains | These domains will not be routinely addressed in this assessment just as in all other previous REAs. Therefore we do not think that specific authors should be specified for these domains |

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| 29 | 5 | Section 1.1 | AOTMiT | As far as I know the MAH of Olysio (simeprevir) is Janssen-Cilag International NV | Janssen represents the pharmaceutical companies of the Johnson & Johnson healthcare company. |
| 30 | 5 | Section 3.0 | IQWIG | The scientific objective of the assessment so far seems ambiguous. We therefore suggest including a formal research question as foreseen in the template for the project plan.<br><br>Furthermore, given the complex nature of hepatitis treatment, e.g. with regard to patient populations or treatment regimens, we would strongly recommend (at the start of the assessment at the latest) to define specific research questions for the different scenarios. This would not only help to understand the planned scope of the project but would also make the preparation and presentation of the assessment easier. In addition, while it seems reasonable to address some of the research questions with subgroup analyses, this will not always be possible and should be known in advance. This is especially true if different patient characteristics lead to different treatment regimens according to the summary of product characteristics (SPC). For example, for ledipasvir/sofosbuvir, in genotype 1 the treatment duration is 12 weeks for patients without cirrhosis and 24 weeks for patients with | We described the objectives indeed in general terms: we specified the molecules that obtained marketing approval from EMA and stated that we would assess combinations of treatments that are recognized in the EPAR. It will depend on the outcome of the search which combinations actually have been studied in or out of the label (and it is not always clear what is in or out of label for some cases).<br><br>A non-exhaustive table with possible combinations and comparators will be attached to illustrate the complexity of this fast moving field today. |

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| | | | | cirrhosis (please see below for example text for ledipasvir/sofosbuvir compared to peginterferon-alfa 2b + ribavirin and Viekirax + dasabuvir, respectively, in patients with genotype 1).<br><br>Suggested wording for the objective of the assessment:<br><br>*The aim of this project is to assess whether the newer treatments of chronic hepatitis C (sofosbuvir, sofosbuvir / ledipasvir, ombitasvir / paritaprevir / ritonavir, dasaburvir, simeprevir, daclatasvir) provide added/less benefits or harms than other treatment options (peginterferon / ribavirin; telaprevir / peginterferon / ribavirin; boceprevir / peginterferon / ribavirin or best supportive care) and against each other.*<br><br>*The assessment will consider the label of the treatments and the analysis will be done for specific genotypes, patient populations and treatment regimens.*<br><br>*The comparison will be performed using direct or indirect comparison, as appropriate.*<br><br>*Specifically, it is planned to assess the following comparisons* [example for ledipasvir/sofosbuvir compared to peginterferon-alfa 2b + ribavirin and | |

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| | | | | Viekirax + dasabuvir, respectively, in patients with genotype 1]*:*<br><br>*ledipasvir/sofosbuvir (LDV/SOF) vs. dual therapy (peginterferon-alfa 2b + ribavirin, PEG+RBV)*<br><br>• *genotype 1 without cirrhosis: LDV/SOF (12 weeks) vs. PEG/RBV (48 weeks)*<br><br>• *genotype 1 with cirrhosis (compensated): LDV/SOF (24 weeks) vs. PEG/RBV*<br><br>*ledipasvir/sofosbuvir (LDV/SOF) vs. dasabuvir (DAS) + ombitasvir/paritaprevir/ritonavir (O/P/R)*<br><br>• *genotype 1b without cirrhosis: LDV/SOF (12 weeks) vs. DAS+O/P/R (12 weeks)*<br><br>• *genotype 1a without cirrhosis: LDF/SOF (12 weeks) vs. DAS+O/P/R+RBV (12 weeks)*<br><br>• *genotype 1b with cirrhosis (comp.): LDF/SOF (24 weeks) vs. DAS+O/P/R+RBV (12 weeks)*<br><br>• *genotype 1a with cirrhosis (comp.): LDF/SOF (24 weeks) vs. DAS+O/P/R+RBV (24 weeks)* | |

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| | | | | • *genotype 1a and 1b, post-liver transplantation: LDF/SOF+RBV (24 weeks) vs. DAS+O/P/R+RBV (24 weeks)* | |
| 31 | 5 | 2.0 Project Introduction/rationale | MoH Malta | As a result, it was decided that WP5 of EUnetHTA will address this need and initiate a joint rapid REA on the new treatment options for Hepatitis C, approved by the European Medicines Agency since 2014. | Thank you for this comment. |
| 32 | 5 | Table 2 | IHS | Change Bristol Meyers Squibb to Bristol Myers Squibb and the Irish Haemophilia Association to Irish Haemophilia Society | They have been corrected. |
| 33 | 5 | Section 1.1. | AETSA | Irish haemophilia association as a patient organisation? | Yes. This will be clarified in the next version. |
| 34 | 6-7 | Section 3.0 | ZIN | The interventions can be better defined, and should include all possible (registered) combinations. The individual compounds are in itself (in most cases) no sensible interventions. I think it is also important to include pegIFN and ribavirine, to e.g. specifically describe interventions such as SOF+pegIFN+RBV and also take into account the (added) efficacy and undesirable effects of pegIFN and RBV. | A non-exhaustive table with possible combinations and comparators will be attached to illustrate the complexity of this fast moving field today. See table with examples of combinations and comparators. |
| 35 | 6-7 | Section 3.0 | ZIN | Intervention/comparisons: I would suggest adding treatment duration or range of treatment | See table with examples of combinations and comparators. |

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| | | | | duration, as described in SPC's and guidelines of each combination | |
| 36 | 6-7 | Section 3.0 | NHS Latvia | In table 3.Project Scope: PICO: section "Interventions" – in accordance with the Summary of Product Characteristics all medicines (sofosbuvir, sofosbuvir+ledispavir, ombitasvir+paritaprevir+ritonavir, dasabuvir, simeprevir, daclatasvir) must be used in combination with other medicines used to treat chronic hepatitis C. Thus for information reasons full combination of drugs used should be indicated. | See table with examples of combinations and comparators. |
| 37 | 6 | Interventions | IQWIG | In some countries only assessments of interventions used according to the label are acceptable. Therefore, the assessment should focus on an analysis of a study pool in which the interventions (and comparators) were used according to the label of the drugs. In addition, a further study pool including all studies, i.e. also studies in which drugs were used outside the label, could be provided, as appropriate for use in countries in which the label is less important. Please clarify this issue in the description of the interventions (and comparators).<br><br>Suggested wording:<br><br>*For all studies it will be described, if the* | We agree with the suggested wording, this has been adapted. |

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| | | | | *interventions (and comparators) were used according to the label of the drugs. An analysis of a study pool in which the interventions (and comparators) were used according to the label of the drugs will be provided. Furthermore, an additional study pool including all studies, i.e. also studies in which drugs were used outside the label, will also be analyzed, as appropriate.* | |
| 38 | 6 | Interventions | | In line 2 ledipasvir is misspelled. Please change ledaspivir to ledipasvir. | It has been corrected. |
| 39 | 6 | Table 3 (study design) | MSD | Evaluate quality of clinical evidence of drug based on comparative head to head active comparator clinical trial data | GRADE will be used to assess the quality of evidence as mentioned in the project document. |
| 40 | 6/7 | Section 3.0 | SMC | Table 3; Interventions.<br><br>I would suggest making it clear that the medicines included under interventions are licensed for administration with other medicines; ie I think it would be preferable to detail the **treatment strategies** rather than the medicines; eg. sofosbuvir + ribavirin (+/- peginterferon), ledipasvir/sofosbuvir + ribavirin, etc. | See table with examples of combinations and comparators. |
| 41 | 6/7 | Section 3.0 | SMC | Table 3; interventions.<br><br>I would suggest making it clear that treatment durations vary depending on genotype, previous | See table with examples of combinations and comparators. |

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| | | | | treatment and presence of cirrhosis. | |
| 42 | 6 | Table 3 (study design) | MSD | Consider adding a factor that would denote a robust development program, i.e. adequate numbers of patients enrolled from relevant subgroups and diverse geography; placebo-controlled trials to facilitate evaluation of safety. | This has been taken into account in the background, but not made explicit. |
| 43 | 6 | 3 Interventions: sofosbuvir (Sovaldi) | MoH Malta | To include: Sofosbuvir must be used in combination with other medicinal products (Pegintereron alfa, ribavirin). | See table with examples of combinations and comparators. |
| 44 | 6 | Interventions: Ombitasvir + paritaprevir + ritonavir (Viekirax) | MoH Malta | To include: Ombitasvir + paritaprevir + ritonavir is always used in combination with other medicinal products such as dasabuvir and ribavirin. | See table with examples of combinations and comparators. |
| 45 | 6 | Line 2 | IHS | Should MSD's Elbasvir and Grazoprevir not be assessed as they are close to registration and may cater for the renal population which is a sub-population that needs to be discussed | In this study, we will only take into account drugs that have already received market authorization from the EMA. These 2 compounds are not yet on the CHMP list of the EMA, and will therefore not be considered in this report. |
| 46 | 6-7 | Section 3.0 | BMS | The project plan does not explicitly state which regimens will be evaluated. The assessment should be limited to regimens that have been approved in EU. | That is correct; the assessment will only address the regimens that are approved in the EU. Local 'off-label' changes cannot be taken into account in this assessment, unless there is published high level evidence supporting the use in clinical |

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| | | | | | practice. See table with examples of combinations and comparators. |
| 47 | 6 | Table 3, PICO-Table | NOKC | Description of the intervention and comparators is not completely consistently reported. | See table with examples of combinations and comparators. |
| 48 | 6 | Table 3, PICO-Table | NOKC | Should you add? : "Ombitasvir + Paritaprevir + Ritonavir is a fixed dose combination product". | It has been adapted accordingly. |
| 49 | 6 | Table 3, PICO-Table | NOKC | Exchange "It is administered orally" with "Ombitasvir + paritaprevir + ritonavir" to avoid misunderstanding that it only refer back to ritonavir. | Has been adapted. |
| 50 | 6 | Table 3, PICO-Table | NOKC | Daclatasvir (DAKLINZA); Exchange "hepatitis C virus" to "HCV" for consistency; Exchange "It is.. " to "Daclatasvir is.." for consistency | Has been adapted. |
| 51 | 6 | Table 3, PICO-Table | NOKC | For comparators mode of action is not described as it is for interventions. It would be useful, both for consistency but also to see if comparisons are fair later on. | Has been added. |
| 52 | 6 | Table 3, PICO-Table | NOKC | It is not stated if you will investigate all doses used in literature of only recommended dose according to SPC. You may want to add a clarification on this. | For all studies it will be described, if the interventions (and comparators) were used according to the label of the drugs. An analysis of a study pool in which the interventions (and comparators) were used according to the label of the drugs will be provided. Furthermore, an additional study pool including all studies, i.e. |

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| | | | | | also studies in which drugs were used outside the label, will also be analyzed, as appropriate. |
| 53 | 6 | Table 3 and table 4b | NOKC | The following text under Outcomes "(include a discussion on the evidence supporting the use of SVR as a valid surrogate for reduction of liver fibrosis progression and reduction of further development of HCC; also discuss role of co-factors (alcohol, cannabis use) and whether SVR has same surrogate value whatever intervention was used to achieve SVR)." should perhaps be moved somewhere else as explanatory text and not an outcome? | Yes, agreed (should be a note under outcome) |
| 54 | 6,7 | Section 3.0 | Lazio | Since the treatment strategy for HCV concerns the administration of multiple drugs (double/triple therapy), including a combination of new drugs with standard treatment (e.g. ribavirin, interferon), the network meta-analysis methods should clearly aimed at including comparisons between different combinations of drugs (when used as interventions or comparators). | This topic has been described in the document; a list of planned analyses is included. |
| 55 | 6 | Section 3.0<br><br>Table 3. Interventions | AETSA | Some interventions can be used in combination with peginterferon and or ribavirin. This is not indicated in the text. | See table with examples of combinations and comparators. |
| 56 | 6 | Section 3.0 | AETSA | Sofosbuvir is a uridine nucleotide analogue that | Has been adapted accordingly. |

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| | | Table 3. Interventions | | inhibits HCV NS5B RNA-dependent RNA<br><br>polymerase, preventing viral replication. | |
| 57 | 6 | Section 3.0<br><br>Table 3. Interventions | AETSA | Suggest rewording "Ritonavir is an HIV aspartic protease inhibitor that increases the bioavailability of<br><br>Paritaprevir by inhibiting its metabolism" as "Ritonavir is not active against HCV. Ritonavir is a CYP3A inhibitor that increases the systemic exposure of the CYP3A substrate paritaprevir". | Has been adapted accordingly. |
| 58 | 6 | Section 3.0 | AETSA | Sofosbuvir and ledaspivir". Correct to "ledipasvir". | Spelling mistake has been corrected. |
| 59 | 6 | Table 3 (interventions ) | AIFA | Please add the posology for each intervention | See table with examples of combinations and comparators. |
| 60 | 7 | Section 3.0 | ZIN | As with the previous comments, I think comparators are better defined in terms of 'real' treatments combinations and not as individual substances. So, for example, TPV+pegIFN+RBV. | See table with examples of combinations and comparators. |
| 61 | 7 | Section 3.0 | ZIN | Comparators are (of course) specific to specific indications (e.g. genotype). | See table with examples of combinations and comparators. |

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| 62 | 7 | Section 3.0 | NHS Latvia | In table 3.Project Scope: PICO: section "Interventions" – in Daclatasvir description replace "It is administered orally" with "Daclatasvir is administered orally" in order to maintain writing style. | Has been changed. |
| 63 | 7-8 | Section 3.0/Table 3 | AOTMiT | Outcomes: in Poland according to current legislation we need LYG and QALY being assessed. 12-week and 24-week SVR, although assessed in the studies, has been criticized as a surrogate end point. We are really happy for a thorough discussion of possible real live added value and scarcities of existing evidence. | This will be part of the discussion. |
| 64 | 7 | Comparators, list of comparators | IQWIG | Our understanding is that the PICO is specifying the research question of the assessment. Placebo is no treatment option in hepatitis C. Therefore, please delete placebo from the list of comparators in the PICO. Alternatively, separate between comparators against which treatment effects according to the research questions should be assessed and comparators which are only accepted as bridging comparators for indirect comparison.<br><br>Suggested wording:<br><br>*In addition to the comparators listed above against which benefits and harms of the* | We did not specify for the moment the inclusion criteria in detail.<br><br>We propose to consider for the moment any study that contains in at least one arm the EMA approved molecules mentioned in the document, with any comparator. Note that this is for the inclusion criteria, not for the research question. It is in theory possible that studies containing only bridging combinations are useful to build a network, in case large and complex networks are planned. However, searching for all possible bridging combination would imply that we identify any study where Hep C is treated, this is not feasible. If constructing a network proves |

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| | | | | *interventions will be assessed, studies covering any other comparator (including placebo) will be used for indirect comparisons, as appropriate.*<br><br>In addition to the PICO for the research question, inclusion criteria for study selection have to be defined. Because, as described above, indirect comparisons will be included as appropriate, study selection should also identify studies with possible bridging comparators beyond the comparators for the assessment. This means that also studies with placebo or other comparators not included in the research question could be selected. However, comparators against which the benefits/harms will be assessed and other comparators merely used for methodological purposes, i.e. as bridging comparator in indirect comparison, should be clearly differentiated. We therefore suggest including both a PICO for the research question and a list of inclusion criteria for study selection in the project plan.<br><br>In addition, a list of inclusion criteria should also cover other aspects (e.g. study type or publication type) which are not part of the PICO for the research question.<br><br>Suggested wording for inclusion criteria (the best | feasible and there are gaps identified, we could do an additional focus search. However, although in theory one should not take this into account in a project document in advance. Most studies are single arm or for our purpose de facto single arm, as even the RCT compare different forms of administration of the same molecule, so it is unlikely that we will be able to construct such a network, at most some 'local' networks will be possible.<br><br>We specified the type of studies. |

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| | | | | format would be a table):<br><br>*Inclusion criterion 1: Patients with chronic Hepatitis C (see scope on patient population)*<br><br>*Inclusion criterion 2 (intervention): Treatment with sofosbuvir, sofosbuvir / ledipasvir, ombitasvir / paritaprevir / ritonavir, dasaburvir, simeprevir, daclatasvir (see scope on intervention)*<br><br>*Inclusion criterion 3 (comparator): Treatment with peginterferon / ribavirin (dual therapy), telaprevir / peginterferon / ribavirin or boceprevir / peginterferon / ribavirin (triple therapy) or with any of the drugs listed under intervention; placebo (or non-treatment) or any other treatment*<br><br>*Inclusion criterion 4: data on relevant endpoints available*<br><br>*Inclusion criterion 5: RCT, non-RCT, prospective observational study, prospective uncontrolled study*<br><br>*Inclusion criterion 6: full publication (including study reports according to ICH E3 or reports fulfilling the requirements of the CONSORT-, TREND-, STARD- or STROBE-Statement, which* | |

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| | | | | *allow for assessment of the study as long as information on study methods and study results is not confidential)* | |
| 65 | 7 | Comparators, rationale | IQWIG | The mere fact that a comparator is used in a clinical trial does not make it a useful comparator for a benefit assessment (please see comment above), please delete this argument. | Agreed, we have deleted this argument. |
| 66 | 7 | Section 3.0 | SMC | Table 3; comparator<br><br>I would emphasize that the comparators of interest are the new treatment strategies, ie, those listed in the interventions section of table 3. | See table with examples of combinations and comparators. |
| 67 | 7 | Interventions: dasabuvir (Exviera) | MoH Malta | To include: Dasabuvir is always used in combination with the combination product ombitasvir + paritaprevir + ritonavir (Viekirax) and in some instances ribavirin is further added. | Has been adapted accordingly. |
| 68 | 7 | Interventions: simeprevir (Olysio) | MoH Malta | To include: Simeprevir must be used in combination with other medicinal products such as with peginterferon alfa and ribavirin or with sofosbuvir. | Has been adapted accordingly. |
| 69 | 7 | Interventions: daclatasvir (Daclinza) | MoH Malta | To include: Daclatasvir must be used in combination with other medicinal products such as sofosbuvir, peginterferon alfa and ribavirin. | Has been adapted accordingly. |

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| 70 | 7 | Comparators | MoH Malta | For consistency of the document, can a very brief drug description for each comparator be included similarly to the Intervention section? | See table with examples of combinations and comparators. |
| 71 | 7 | Section 3.0 Table 3.Comparison | AETSA | Ribavirin (REBETOL, RIBAVIRIN MYLAN, RIBAVIRIN TEVA) Ribavirin is<br><br>used orally, in combination with other treatments. | Has been adapted accordingly. |
| 72 | 7 | Section 3.0<br><br>Table 3.<br><br>Outcomes | AETSA | Add Outcomes for effectiveness: relapse, cirrhosis, hepatocellular carcinoma, liver transplantation | Agreed, we have added this. Apart from relapse, there is only indirect evidence from the natural history of the disease, KCE plans to incorporate this information in a modelling exercise, but not in the scope of this EUnetHTA project |
| 73 | 7 | Comparison | ASSR | For the second comparator no genotype is specified | Has been added. |
| 74 | 7 | Table 3 (comparison) | AIFA | Please add the posology for each comparator | See table with examples of combinations and comparators. |
| 75 | 7 | Table 3 (comparison) | AIFA | Please reword the bullet point referred to ribavirin: "ribavirin (REBETOL, RIBAVIRIN MYLAN, RIBAVIRIN TEVA. Ribavirin is used orally and in combination with other anti hepatitis C medicines." | Has been changed according to your and other reviewers' comments. |

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| 76 | 7 | Table 3 (comparison) | AIFA | For the sake of consistency with other interventions, please add the genotypes for ribavirin. | Has been added. |
| 77 | 7-8 | Section 3.0 | BMS | One important effectiveness measure that is not listed but which has an impact on the clinical utility of HCV regimens, especially in co-infected populations, is drug-drug interactions. | Agreed. It will be mentioned if studied and clinically relevant, e.g. in HIV coinfection. |
| 78 | 8 | Section 3.0 | ZIN | Subgroup analyses: I suggest to fully use the METAVIR classification and not just cirrhosis y/n, since F0 is (might be) associated with better outcomes than higher stages. Decompensated cirrhosis could also be added as a specific subgroup. | F0 is not always analyzed separately from other fibrosis stages and elastography does not provide clear cut answers. However, if data are available F0 will be analyzed separately |
| 79 | 8 | Endpoints | IQWIG | The inclusion of SVR24 and SVR12 as (possible) valid surrogates for late complications seems reasonable. However, depending on the stage of the disease, the validity of SVR as a surrogate for some of the listed outcomes may differ. For example, in patients with cirrhosis SVR obviously is not a valid surrogate for progression of fibrosis. With respect to the discussion of the evidence supporting the use of SVR as a valid surrogate, we therefore suggest to address different stages of the disease, e.g. without cirrhosis, with compensated cirrhosis, with decompensated cirrhosis and post-liver | Ok, we will adapt as suggested. |

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| | | | | transplantation.<br><br>Suggested wording:<br><br>…also discuss role of co-factors (alcohol, cannabis usr), *role of stage of disease (without cirrhosis, with compensated cirrhosis, with decompensated cirrhosis, post-liver transplantation)* and whether SVR has same surrogate value whatever intervention was used to achieve SVR. | |
| 80 | 8 | Endpoints | IQWIG | It is unclear to us why "rapid virological response" would be an endpoint in routine care. Treatment should be given for the time periods specified in the SPC and treatment success would be evaluated based on SVR. We suggest deleting this endpoint. | Ok, we will adapt as suggested. |
| 81 | 8 | Endpoints: rationale | IQWIG | The mere fact that an endpoint is commonly used in clinical trials does not make it a relevant endpoint; please delete this argument. | Agreed, we have deleted this argument. |
| 82 | 8 | Subgroups | IQWIG | We would suggest adding baseline HCV RNA and baseline fibrosis stage. From previous studies it is known that these factors may be associated with different outcomes for SVR. | Ok, we will adapt as suggested. |
| 83 | 8 | Section 3.0 | JnJ | **Outcomes for effectiveness:** | To be mentioned if studied and clinically |

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| | | | | - Development of and persistence of resistance , including cross-resistance | relevant. |
| 84 | 8 | Section 3.0 | JnJ | **Outcomes for safety:**<br><br>- Drug-Drug-Interactions | To be mentioned if studied and clinically relevant. |
| 85 | 8 | Section 3.0 | JnJ | **Subgroups analysis**<br><br>In line with recent developments in the field of HCV and updates of clinical guidelines, we suggest to take out 2 subgroups (that were relevant with the older agents) and include 2 new ones (that are proving to be relevant with the newer agents)<br><br>Take out :<br><br>- People who are intolerant to or ineligible for interferon treatment.<br><br>This was a regulatory limitation imposed on the first interferon-free treatment available for G1 patients (simeprevir plus sofosbuvir), largely driven by the small number of patients on which the regulatory approval was based. For simeprevir plus sofosbuvir , recently , EMA/CHMP has agreed to remove this restriction, by approving variation | Agreed.<br><br>It depends how you see the subgroup analysis: a number of studies are done on people who are intolerant or ineligible for treatment, and it is unclear on forehand if these studies can be pooled with others or need to be treated separately. It may be useful to asses this in a subgroup analysis. |

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| | | | | EMEA/H/C/002777/II/0012 - effective end July, based on more ample clinical evidence available meanwhile.<br><br>- Presence or absence of IL28B polymorphism (in INF-based regimens)<br><br>Include :<br><br>- presence or absence of baseline resistance (Ns5A, Ns3)<br><br>- geno-subtype (G1a, G1B, G4, ..)<br><br>Further specify :<br><br>- Presence or absence of cirrhosis, including decompensated cirrhosis | |
| 86 | 8 | Section 3.0 | ELPA | Also discuss role of co-factors (alcohol, cannabis<br><br>use) and whether SVR – new (alcohol, medication for other diseases, cannabis) and …. (because of drug-drug interaction) | This topic will be part of the discussion section. Very important indeed when it comes to modeling long term outcomes. |
| 87 | 8 | Table 3 – Outcomes section | IHS | A comparison of SVR 12 vs. SVR 24 would be suggested to ensure that SVR12 is sufficient for treatment success | This is planned. Should be part of the endpoint discussion also. |

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| 88 | 8 | Table 3 – Subgroups section | IHS | Additional sub groups for Renal Patients based on the limited effectiveness of drugs for these patients. Patients with significant fatigue issues may also be considered as suggested in the AASLD guidelines from the US. May also consider a haemophilia patient sub-group. These patients historically had a higher rate of under-going IFN therapies, good adherence rates and lower response rates. With new DAA's access and tolerability should be easier and all patients have been infected for excess of 25 years. | In addition to HCV genotype/subtype, specific analyses are planned if data are available (no cirrhosis, cirrhosis with or without decompensation, post-transplant, naïve or non responder, coinfection, etc,). This will be driven by the available data. |
| 89 | 8 | Table 3 – Study Deign section | IHS | I would suggest including registries as due to the initial high costs of these drugs some countries have set up specific registries such as ICORN in Ireland. This information is being used to look at the effects of treatment as well as methods for prioritizing patients | Thank you for this suggestion. We agree that registries are important but currently the information on the new therapies is not available in the registries. We assume that in a few years sufficient data become available from these registries which can be used in possible reassessments. |
| 90 | 8 | Section 3.0 | BMS | The proposed effectiveness measure "The *proportion of the infected population that is willing to start treatment in routine care*" is not clearly defined and is not a standard outcome in HCV trials. | Agreed that this is not a standard outcome but it cannot be denied that it is highly relevant given the low proportion of hepatitis C patients that was willing to undergo IFN based treatment. Can be put under discussion. |
| 91 | 8 | Section 3.0 | BMS | The proposed effectiveness measure, *mortality*, is a long term outcome that is not possible to | Although we acknowledge that mortality as a long-term outcome might not have been |

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| | | | | measure as an effectiveness outcome in standard HCV trials. It is measured as a function of disease progression via modeling which is outside the scope of this project. | assessed in clinical trials, it is a patient-relevant outcome and therefore will be reported; if it has not been reported in clinical trials, it will allow us to highlight evidence gaps that should be addressed in future clinical trials. |
| 92 | 8 | Section 3.0 | Lazio | The subgroups analysis should be extended. In particular: i) the effect of severity of the disease on outcomes should be tested (e.g. by stage of disease); ii) the effect of time of HCV diagnosis on outcomes should be tested; iii) the effect of different genotypes (and related treatment combinations/options) on outcomes should be tested. | In addition to HCV genotype/subtype, specific analyses are planned if data are available (no cirrhosis, cirrhosis with or without decompensation, post-transplant, naïve or non responder, coinfection, etc,). |
| 93 | 8 | Section 3.0<br><br>Table 3.<br><br>Subgroups analysis | AETSA | Add Subgroups analysis:<br><br>- Different HCV genotypes, and genotype subtypes<br><br>Different stages of fibrosis | In addition to HCV genotype/subtype, specific analyses are planned if data are available (no cirrhosis, cirrhosis with or without decompensation, post-transplant, naïve or non responder, coinfection, etc,). |
| 94 | 8 | Section 3.0<br><br>Table 3.<br><br>Subgroups analysis | AETSA | To establish difference among cirrhosis subgroups: compensated, advanced compensated and decompensated cirrhosis | We will address patients with compensated and decompensated cirrhosis as suggested in the SPC by EMA. In addition to HCV genotype/subtype, specific analyses are planned if data are available (no cirrhosis, cirrhosis with or without decompensation, post-transplant, naïve or non responder, coinfection, etc,). |

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| 95 | 8 | Section 3.0<br><br>Table 3.<br><br>Study design | AETSA | Will systematic reviews, meta analysis and health technology assessment reports be included? | It is not planned to systematically include all published systematic reviews, meta-analysis, and HTA reports. According to the pre specified study design section of our PICO table we will include randomized controlled trials, non-randomized controlled trials, prospective observational studies and prospective uncontrolled trials. However, if available and feasible we might want to update a recent, high quality systematic review with recently published clinical trials. |
| 96 | 8 | Outcomes for effectiveness | ASSR | Sustained Virological Response after 12/ 24 weeks (SRV12- SVR24) are "traditional" endpoints for evaluating current treatments. Can't hard endpoints – better capturing the supposed added therapeutic value – be included (if they have not been evaluated in the trials, the research / knowledge gap will be highlighted) | In the discussion this should be highlighted indeed. E.g. HCV RNA that is detectable but is below cut-off is considered SVR in the trials; which is questionable. Fortunately this is the exception to the rule. |
| 97 | 8 | Outcomes for effectiveness :The proportion of the infected population that is willing to start treatment in | ASSR | Please specify how this endpoint has to be recorded in the trials in order to be assessed. | We agree that this is not a standard outcome but believe that it is highly relevant given the low proportion of hepatitis C patients that was willing to undergo IFN based treatment. Can be put under discussion. |

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| | | routine care | | | |
| 98 | 8 | Outcomes for effectiveness :<br><br>• Rapid virological respons<br><br>Development of resistance | ASSR | Please specify how these outcomes should be defined and measured in the trials in order to be considered in the assessment | This is no longer an outcome |
| 99 | 8 | Outcomes for effectiveness :<br><br>Health-related quality of life | ASSR | Please specify which questionnaires are considered suitable for measurement of QOL in these patients | There are several questionnaires available to assess quality of life in hepatitis C patients, such as short form-36 (SF-36), chronic liver disease questionnaire (CLDQ), hepatitis quality of life questionnaire (HQLQ), liver disease quality of life questionnaire (LD QOL), or liver disease symptom index 2.0 (LDSI 2.0). We have not restricted assessment of QOL to any specific of these questionnaires. For later economic modelling, which is not a part of this assessment, EQ5D remains a preferred option. |
| 100 | 8 | Outcomes for effectiveness | ASSR | Please consider the opportunity of including the following additional outcomes:<br><br>- incidence of liver transplantation | Liver transplantation volume is determined by many variables, would indeed be interesting to see a decrease in the need for transplant. However, better endpoints could be decompensated cirrhosis and HCC indeed, |

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| | | | | - incidence of hepatocarcinoma<br><br>- incidence of hepatic failure | which are driving the need for transplantation. |
| 101 | 8 | Outcomes for safety | ASSR | For the sake of transparency, a list and description of AEs and SAEs that Authors are going to look for should be added | We look initially for all reported AE |
| 102 | 8 | Table 3 (outcomes) | AIFA | Since alcohol and cannabis use cannot be the only co-factors, please add etcetera. | Agreed. |
| 103 | 8 | Table 3 (outcomes) | AIFA | Please add "Relapse rate" | Relapse after SVR12/24 was added. |
| 104 | 8 | Table 3 (outcomes) | AIFA | There is an inconsistency between the PICO and assessment elements Table (page 13). In fact in the assessment table it is reported that the effect on the mortality is not relevant for this project, whereas in the PICO mortality is considered among outcomes. | Will be corrected. |
| 105 | 8 | Table 4 (sub-groups analysis) | AIFA | The absence of cirrhosis should be differentiated also in terms of liver fibrosis, as well as the presence of cirrhosis should be detailed in terms of severity (e.g. Child classification). As subgroup people with hepatocellular carcinoma (HCC) should be included. | The studies will indicate what level of detailed analysis is possible. |

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| 106 | 9 | Table 4a | EFPIA | As this analysis concerns products already available on the market, any project should consider all available evidence. EFPIA considers that focusing on RCTs and only "maybe discuss additionally" real world information is not sufficient. | Real world information is essential to consider also. |
| 107 | 9 | Section 4.0 | ZIN | With regard to single arm studies, I feel that a discussion is necessary why this (generally considered low level of evidence) is acceptable. Obviously, a thorough analyses of limitations/uncertainty/risk of bias of inclusion of these studies should be included. | Indeed, only acceptable for breakthrough innovations such as this one; head to head trials will remain essential in those groups where response is not 100% in trials or real-life cohorts. |
| 108 | 9 | Section 4.0/Table 4a | AOTMiT | Any real world data should be sought as the existing evidence in the RCT is for the period too short compared to live-long outcomes expected | Agreed. |
| 109 | 9 | Table 4a | IQWIG | We would like to suggest not limiting the search to publications in English language. | Ok, we will adapt as suggested. |
| 110 | 9 | Table 4a | IQWIG | Please refer to the new EUnetHTA guideline on Information retrieval (the final version of the EUnetHTA Guideline will be published in the end of June, beginning of July)<br><br>"A systematic literature search (not limited by publication date but limited to English language) will be performed according to ~~the Cochrane~~ | Ok, we will adapt as suggested. |

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| | | | | ~~methodology [6]~~ the EUnetHTA guideline on Information retrieval [EUnetHTA 2015], on standard medical and HTA databases."<br><br>*Citation*<br><br>*European network for Health Technology Assessment. Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness. http://www.eunethta.eu/news/closed-public-consultation-draft-methodological-guideline-process-information-retrieval-systema*<br><br>http://www.eunethta.eu/news/closed-public-consultation-draft-methodological-guideline-process-information-retrieval-systema | |
| 111 | 9 | Table 4a | IQWIG | The reasons why clinical trials registries will be assessed should be extended. Besides the study status (ongoing, completed, etc.) the assessment should not be restricted to clinical trials where results are available.<br><br>Suggested wording:<br><br>*"…for registered **completed,** ongoing **and withdrawn** clinical trials or results posted: …."* | Agreed, this is how it was done for sofosbuvir trials. |

**EUnetHTA JA2 WP5 – STRAND A**
**Public Consultation: Comments and Author's replies on the Draft Project Plan on 'Rapid Relative Effectiveness Assessment of new pharmaceuticals for the treatment of chronic hepatitis C'**

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| 112 | 9 | Table 4a | IQWIG | We do not think it is necessary to search ISRCTN and mRCT. ISRCTN is included in ICTRP Search portal, mRCT is not accessible at the moment (http://www.isrctn.com/page/mrct) | We will be using WHO ICTRP in this study. |
| 113 | 9 | Table 4a | IQWIG | Please add "Regulatory documents" as a further source to identify relevant studies<br><br>Regulatory authorities (e.g. EMA, FDA) publish sections of reports prepared during the approval process. These documents can offer important insights into clinical studies and may also include a list of studies that are potentially relevant for a systematic review. | Indeed, important source sometimes. We will adapt as suggested (EPAR) |
| 114 | 9 | Table 4a | IQWIG | As a preparation for the review of the draft report we would like to point out that the reviewers would need to be provided with sufficient information and documentation on the information retrieval process to be able to conduct their review.<br><br>In order to obtain a reproducible and transparent assessment to rely on, the process and the results of the systematic literature search need to be fully documented. This means the following | This will be included in this assessment. |

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| | | | | documents and files are required:<br>- The search strategies for each database (date of search, interface or database segments used, etc.)<br>- RIS files [1]of the hits for each search (bibliographic database and clinical trial registries) and each source (Medline, clinicaltrials.gov, etc.)<br>- List of excluded references (on full text level) with reason for exclusion (bibliographic databases)<br>- List of excluded references with reason for exclusion (study registries)<br>- Full texts<br>( RIS: Research Information System Format; standardized file format for reference management and export of bibliographic data) | |
| 115 | 9 | Table 4a | IQWIG | Again as a preparation for the review of the draft assessment report and for transparent data presentation, we would like to suggest that the report provides a table with the included primary studies. The different sources available for each study should be displayed in detail (clinical study | This is planned and standard procedure for KCE. |

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| | | | | report, trial registry entry, publication etc.). | |
| 116 | 9 and 21 | Table 4a and 7.0 | IQWIG | The EUnetHTA guideline on information retrieval recommends including clinical study reports (CSR) in the assessment. In the project description it is not clear how retrieval and use of CSR will be handled and what conclusions are drawn if no CSR are provided. We strongly recommend including queries to manufacturers in order to obtain clinical study reports as part of information retrieval. | We plan to contact the manufacturers to obtain study reports for those studies without results reported as full publication. |
| 117 | 9 | Section 4.0, Table 4a | IQWIG | Comment on methods for indirect comparison:<br><br>When conducting indirect comparisons and network meta-analyses it is essential to evaluate the underlying assumptions of similarity, homogeneity and consistency. According to the project plan "…clinical and statistical heterogeneity, the extent to what the studies are interrelated and transferrable through a comparison group that is sufficiently similar, both in intervention and in population.", will be taken into account which corresponds to the similarity and homogeneity assumption.<br><br>We suggest describing the planned approaches and its implications more precisely. How will the similarity be investigated and what will be the proceeding, if the studies are found being not | For clinical and statistical heterogeneity, we follow the Cochrane guidance.<br><br>If studies can be pooled is a judgement based on clinical, methodological and statistical grounds.<br><br>We refer to the methods described in Cochrane Comparing Multiple Interventions Methods: Background document Stream 2 (Statistical issues in NMA). Statistical methods for assessing heterogeneity in NMA are diverse and provide statistics that are to a large degree equivalent to either a Q or an I2 statistic, but little is known about their power. In our case, even if a NMA is possible, power to detect heterogeneity in the network will be limited. |

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| | | | | similar? The same applies to homogeneity. It should be clarified what kind of statistical method (e.g. Q statistic for all pairwise comparisons) and what cut-off will be used to investigate homogeneity. What will be the proceeding, if meaningful statistical heterogeneity is identified? According to standard methodology, it would not be adequate to pool study results, if there is meaningful statistical heterogeneity. Potential effect modifiers, which will be investigated as potential reasons for heterogeneity, should be defined a priori.<br><br>From our point of view, it should also be described how the consistency assumption will be evaluated and what the implications of inconsistency in the network would be. | The only effect modifiers that we see on forehand are the ones determining the subgroup analysis, of which we provided a list that will be expanded with the factors suggested in this list<br><br>It is no good practice to simply define heterogeneity using a cut off point for the Q statistic or I2 statistic, which is after all only a transformation of the Q statistic and the degree of freedom, in the case of pairwise comparisons. There is no valid ground to do so, as both Q and I2 depend on several factors, including the power of the study. It can only serve as an element in the judgement on whether and how to pool (random effects or not). |
| 118 | 9 | Section 4.0, Table 4a | IQWIG | The second paragraph states "On safety outcomes, synthesis will be limited to qualitative synthesis of the data". From our point of view, it seems inappropriate to treat safety outcomes different from efficacy outcomes. Therefore, we suggest deleting this statement. | We agree. |
| 119 | 9 | Section 4.0, Table 4a | IQWIG | Comment on use of single arm trials:<br><br>According to the project plan "randomized controlled trials, single arms trials" will be included in the clinical effectiveness and safety | Single arm trials will only be used in a descriptive way, we will not pool them. We cannot use them to directly compare molecules. |

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| | | | | domains. The role of single arm trials so far is unclear from the methods section. Please describe how single arm trials will be used in the comparative analysis. Please state any additional methodological consequences of using single arm trials (please see suggestions below).<br><br>The statements given on single arm trials in the context of indirect comparisons and meta-analyses (in the last paragraph of page 9) seem to contradict earlier statements. We agree that single arm trials (and observational studies) should not be included in network meta-analysis or in pairwise meta-analysis of RCTs. If and only if no other evidence is available, a naïve indirect comparison of using all available suitable single arm trials provides an option, see the following comment. Please clarify the use of single arm trials in the different analytical scenarios. | |
| 120 | 9 | Section 4.0, Table 4a | IQWIG | Comment on use of different study types:<br><br>Overall, from our point of view it does not become clear how the different study types which are planned to be included will be handled and analysed. Is there, for example a hierarchy of evidence?<br><br>From our point of view for pairwise comparisons | We explicitly state we will not integrate single arm studies and observational studies into the network meta-analysis. The hierarchy of evidence is very well in theory, but a network analysis integrates both direct and indirect evidence all based on RCT's. We can add that if RCT provide a sufficiently precise estimate we will use this as a base. It should be noted that most RCT's actually compare different durations, |

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| | | | | meta-analysis of RCTs should be considered in the first place. If a meta-analysis of RCTs is available for a given scenario, no other study types (non-randomised studies, observational studies, single arm trials) should be taken into account. If only single arm trials exist, a naïve indirect comparison (historic comparison) could be considered, but results should be interpreted with caution and only if they show dramatic effects (*Glasziou P, Chalmers I, Rawlins M, McCulloch P. When are randomised trials unnecessary? Picking signal from noise. BMJ 2007; 334(7589): 349-351.*). Other study types than RCTs should also not be integrated into network meta-analysis.<br><br>From our point of view it should also be stated a priori on what basis a pairwise comparison will be evaluated, if both direct evidence and indirect evidence (from network meta-analysis or naïve indirect comparison) are available. Which estimate will be used as the base of conclusions? | different formulations and combinations with or without ribavirin. Comparing these is not the focus of our report, so even RCT's found will only contribute the same information as single arm RCT's.<br><br>Observational studies, in a real life setting, provide a different kind of information, on the effectiveness as in contrast to efficacy, and will be included even if there are precise estimates from RCT's and will be taken into account when evaluating the evidence on which our conclusions are based.<br><br>If both direct evidence and indirect evidence from network meta-analysis exists, direct evidence is dominant, but indirect evidence will be used if direct evidence lacks precision (meaning if confidence intervals are too wide or study quality is too low).<br><br>Basing our conclusions on naïve indirect comparisons alone would be a major problem but it is very likely that this will be the case, as most studies are single arm or de facto single arm. An option is to use a predefined historical threshold, but this is difficult to do in advance without a search and analysis of the existing evidence and thorough discussion with content |

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| | | | | | experts.<br><br>We can address these issues in the project plan but it will be difficult to provide a solution. |
| 121 | 9 | Section 4.0, Table 4a | IQWIG | We suggest describing the statistical methodology to be used in more detail.<br><br>What kind of model (fixed or random effects) is planned for the analysis? For network meta-analysis a random effects model is more useful and more common. Therefore, we suggest random effects models for all analyses to preserve consistency for the different analyses.<br><br>What effect measures will be used for the different outcome types?<br><br>We suggest to add the following section to the project plan for pairwise meta-analysis:<br><br>*For statistical analyses, data from intention-to-treat analyses will be used, if provided in the identified documents. Meta-analyses will be carried out on the base of random effect models [DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7(3):177-188.]. If data for mean and variance are not available, these will be estimated or approximated from published data if possible.* | We refer to the Cochrane guidance and we plan to analyze according to their recommendations.<br><br>We do not see the added value of adding some generic synopsis of these in the project plan;<br><br>In absence of statistical heterogeneity random and fixed effects give numerical the same results, especially if DerSimonian is used.<br><br>We will not use a predefined threshold for heterogeneity, for reasons explained above. |

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| | | | | *For continuous data, mean differences will be calculated, when indicated using the standardization with Hedges' g. For binary data, relative risks will be calculated.*<br><br>*Effect estimates as well as confidence intervals will be displayed using forest plots. Statistical heterogeneity will be assessed using the measure $I^2$ and the statistical test for heterogeneity [Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557-560.]. If substantial heterogeneity is identified ($p \geq 0,20$ for the test of heterogeneity), pooled estimates will not be displayed. Additionally, the following potential effect modifiers will be analysed to identify potential reasons for heterogeneity: [please specify potential effect modifiers, these can be methodological or clinical factors]*<br><br>A similarly detailed description of methodology is also required for network meta-analysis. | |
| 122 | 9 | Table 4a | MSD | Due to a lack of H2H trials, network meta-analyses (NMA) would be a key part of the assessment. Exclusion of observational cohort studies and single arm studies may limit the ability to conduct robust NMA. | In our opinion, NMA using cohort and single arm studies is experimental at best, fraught with methodological problems and unlikely to be robust. The decision to conduct an NMA will depend on the trials we find. |

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| 123 | 9 | 4 Project Approach and Method | MoH Malta | Could not find the full definition of the acronym SR. | We will write Systematic Review (SR) in full when first used in the document. |
| 124 | 9 | Section 4.0 | BMS | The project plan indicates that the EPAR is a source of data. The EPAR is continuously updated with new data being submitted. It would be helpful to specify which version of the EPAR would be accessed. | This will be clarified in the next version. |
| 125 | 9 | Section 4.0 | BMS | The project plan states: "Observational cohort studies and single arm studies will not be integrated neither into a network nor a classic meta-analysis, following the Cochrane guidance on systematic reviews." This may result in a very limited number of possible comparisons, especially comparisons of new oral DAA agents with one another. Most of these agents have been studied in single arm trials. | In our opinion, NMA using cohort and single arm studies is experimental at best, fraught with methodological problems and unlikely to be robust. |
| 126 | 9 | Table 4a | NOKC | It is not clear for me if two reviewers will assess publications from the systematic search and the records form assessing registries for clinical trials or just the systematic search. | Two reviewers will assess publications from the systematic search but not from the trial registry |
| 127 | 9 | Table 4a<br><br>Table 5 | NOKC | I wonder about this statement "On safety outcomes, synthesis will be limited to a qualitative synthesis of the data". In table 5 you list your research questions as such "what is the | This statement was deleted. |

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| | | | | frequency…"<br><br>As far as I can tell, this will give you the possibility presenting results quantitatively for example in meta-analysis (depending on reporting in studies of course).<br><br>Could you add a clarification of your choice of method of qualitative synthesis? | |
| 128 | 9 | Table 4a, 3rd paragraph | ASSR | Could the addition of the following clinical trial registry: http://public.ukcrn.org.uk/search/ be taken into consideration? | We limit the search to the WHO portal |
| 129 | 9 | Table 4a, 6th paragraph | ASSR | Please explain the meaning of "randomized controlled trials, single arms" | Section has been adapted. |
| 130 | 9 | Table 4a Line 2 | AIFA | Please add clinical guidelines | The assessment report will not include references to clinical guidelines. |
| 131 | 10 | Section 4.0 | ZIN | "Diagnosis" is a bit vague. It is important to extract all relevant patient characteristics as described in PICO | We don't fully understand this comment, but have added some text. |
| 132 | 10 | Section 4.0 | ZIN | "Intervention": also include treatment duration | We agree, has been adapted. |
| 133 | 10 | Table 4b, extraction for primary | IQWIG | For data interpretation and to be able to assess suitability of outcomes for indirect comparisons, information on endpoint operationalization | We agree, has been adapted. |

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| | | studies; outcomes and follow-up | | (endpoint definition) and duration of observation (follow-up time) for each endpoint is required. Please clarify this for data extraction.<br><br>Suggested wording:<br><br>*Efficacy outcomes (endpoint definition, duration of follow-up, study results)*<br><br>*Safety outcomes (endpoint definition, duration of follow-up, study results)* | |
| 134 | 10 | Table 4b, extraction for primary studies; outcomes and follow-up | IQWIG | From our point transparency of the assessment is crucial for its quality and acceptability. We therefore would like to suggest clarifying, that all information used in the assessment will be made publicly available in the assessment report.<br><br>Suggested text:<br><br>*All information on study results and study methods which is used for the assessment will be made publicly available in the assessment report.* | We agree, has been adapted. |
| 135 | 10 | Section 4.0 | BMS | The preliminary evidence or extraction table (Table 4b). is missing important baseline characteristics such as genotype, fibrosis level, co-infection. Only trials that are comparable in | We agree, has been adapted. |

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| | | | | these ways should be used for comparisons | |
| 136 | 10 | Table 4b | NOKC | You indicate that you will extract Authors conclusions from the publications and give your comments. I wonder if that is necessary. As long as you extract the actual results, and use risk of bias and GRADE the information will be available for the readers elsewhere. | We agree, has been adapted. |
| 137 | 10 | Section 4.0<br><br>Table 4b | AETSA | Add as information to be extracted from included primary studies:<br><br>- Patients groups: comorbidities, proportion of participants with different HCV genotypes, different stages of fibrosis, response to previous treatment (non-response, partial response, relapse).<br><br>- *Intervention* including dosing, frequency and duration information.<br><br>- *Comparators* including dosing, frequency and duration information.<br><br>- *Outcomes and follow-up:* type of analysis (intention to treat or per protocol) | Agreed, withdrawals before first treatment is relevant as this may be higher if randomized to IFN containing arm in open label RCT |

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| | | | | - *Withdrawals* | |
| 138 | 11 | Section 4.0 | ZIN | Extraction of efficacy data is incomplete: should follow PICO | We agree, it has been adapted |
| 139 | 11 | Section 4.0 | ZIN | Table 5, technology: perhaps better to describe at a higher level first, e.g. from virology to different pharmacological classes to specific treatments. | We don't fully understand this comment. Assessment elements are pre specified in Core Model for Rapid REA. |
| 140 | 11 | Efficacy outcomes | IQWIG | It is unclear why the presentation of benefit outcomes is separated between SVR (listed separately even for different observation periods) and other outcomes (listed as one bullet with the qualifier "as far as directly assessed"). This might be understood as a ranking for which no rationale is provided.<br><br>Furthermore, the list is not consistent with the endpoints listed in the scope.<br><br>Please list all relevant endpoints in a list with one bullet for each endpoint. Please ensure consistency with the scope. The clarification that effects on these endpoints are only considered if directly measured in the trials could be added below the list (this would be true for all endpoints). | We agree, has been adapted. |

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| 141 | 11 | Efficacy outcomes | IQWIG | Treatment completion: It is unclear why this would be an efficacy endpoint. We suggest deleting this endpoint. | We agree, and have deleted this endpoint. |
| 142 | 11 | Section 4.0 | JnJ | **Description and technical characteristics of technology**<br><br>A0020 Mandatory element : Regulatory Status<br><br>**For which indications has the technology received marketing authorisation or CE marking?**<br><br>Recently 2 type II variations regarding the SmPC of simeprevir were approved and received positive CHMP opinion (EMEA/H/C/002777/II/0012 and EMEA/H/C/002777/II/0007/G). The SmPC is in the process of being updated , and is expected to be finalized and available end July 2015. Especially the first variation (0012) is important for the scope of this REA project , as it is removing the population restriction initially imposed on the use of simeprevir in combination with sofosbuvir . Thus simeprevir + sofosbuvir is no longer restricted only to people who are intolerant to or ineligible for interferon treatment. | Thank you for this additional information, it will be taken into account in our assessment. |
| 143 | 11 | Section 4.0 | ELPA | Efficacy: please add here again other medication | In our opinion, drug drug interactions are a |

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| | | | | because of drug-drug interaction | mechanism leading to efficacy or safety issues but we will not consider it as an outcome itself. |
| 144 | 11 | Table 4b | IHS | A comparison of SVR 12 vs. SVR 24 would be suggested to ensure that SVR12 is sufficient for treatment success | This should be under discussion section of outcomes (including relevance of SVR for long term outcomes). |
| 145 | 11 | Table 4b – B003 | IHS | If MSD drugs are included this section will need to be updated | Please see our earlier reply, thank you. |
| 146 | 11 | Table 5 | NOKC | There is inconsistency in how you present/identify assessment elements research questions when more than one questions is formed for one id, example A0002 and D0006. It may be easier to clearly define questions if you label them with the id number and a), b) etc. | When more research questions are presented we will identify them accordingly. |
| 147 | 11 | Table 5, D0001 | NOKC | Mortality is assessed as no relevance. However, it is part of the scope in table 3 and 4b. (see outcomes)<br><br>Please select one option and update. | Provide data on mortality associated to HCV is relevant. It helps to clarify HCV impact on society. Mortality is of course an important outcome, but probably there are no study results available yet. |
| 148 | 11 | C0002 | NOKC | Are the harms related to dosage or frequency or administration of sofosbuvir+ledipasvir; sofosbuvir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir; simeprevir in relation to the comparators? | Partial changes have been made. |

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| | | | | Suggested rewording:<br><br>Is there a dose-response relationship with respect to harms for sofosbuvir+ledipasvir; sofosbuvir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir; simeprevir or the comparators? | |
| 149 | 11 | Table 6<br><br>Introductory text line 5-7 | NOKC | "The final rapid relative effectiveness report will present potentially relevant assessment elements from the HTA Core Model from these domains, to provide guidance for the user on a national level."<br><br>Just to be absolutely clear, you may want to add: "The suggested assessment elements will not/ will *(choose your option)* be answered within this report" | Suggested text was added. |
| 150 | 11 | Section 7, line 10 | NOKC | The MAH is asked to provide an expert who can be a point of contact to the authors and answer questions throughout the assessment.<br><br>Suggested rewording:<br><br>The MAH is asked to provide *a clinical* expert *in the field of Hepatitis C treatment* who can be a point of contact to the authors and answer questions throughout the assessment. | The suggestion is noted, however, questions may not only be clinical, but also methodological. Wording was not changed. |

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| 151 | 11 | Section 4.0 | Lazio | Subject not responding (lack of efficacy) to treatment combinations should be also described and evaluated as a potential safety/efficacy issue. | The SVR result will reflect those subjects. Indeed, subjects without SVR remain a possible source of transmission of HCV. |
| 152 | 11 | Section 4.0 - Table 4b Outcomes | AETSA | Outcomes contained in the "Outcomes" element of the PICOS is not entirely consistent with the information identified in table 4a. | We have checked the congruency and will adapt if needed. |
| 153 | 11 | Table 5 (AE: *B0002)* | AIFA | In this assessment element the claimed benefit of different products should be compared not only in relation to the comparators, but also to each other. It is suggested to change the wording of the AE in<br><br>What is the different claimed benefit of sofosbuvir+ledipasvir; sofosbuvir; daclatasvir;<br><br>ombitasvir + paritaprevir + ritonavir; dasabuvir; simeprevir and in relation to the comparators and one in comparison to each other? | Agreed. |
| 154 | 12 | A0002 | ELPA | Please add: What are the incidence and prevalence of the<br><br>HCV?<br><br>Figures in EU if possible per genotype, age | This information has been reported earlier in the report. |

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| | | | | group, risk groups, figures per country. | |
| 155 | 12 | Table 4b – B009 | IHS | Should this section not be a yes as there are many additional drugs and assessment tools required for the treatment of side-effects for IFN based treatments? | We have not changed this because of possible overlap with B0008. |
| 156 | 12 | Table 4b – A0021 | IHS | Extremely important and should be broken down by country | We will envisage data presenting by countries, if possible. |
| 157 | 13 | Section 4.0 | ZIN | Mortality: is included in PICO, appears to be in contradiction with this section. "Clinical effectiveness" assessment should follow PICO. | Mortality is of course an important outcome, but probably there no study results available yet. |
| 158 | 13 | Table 4b – D0003 | IHS | This may be of some interest when assessing using DAA's in situations where a patient is actively using drugs or alcohol. A comment at least is appropriate | If specific studies are identified they will be included, if not it will be a topic in the discussion section. |
| 159 | 13 | Table 4b – D0011 and D0016 | IHS | If IFN is being assessed as a comparator these sections will be required | These are non-mandatory elements. |
| 160 | 13 | Section 4.0<br><br>Table 5 | AETSA | Mortality is said not to be planned in this project, but the mortality outcome is going to be assessed? | We agree that mortality is an important outcome, but probably there are no study results available yet. |
| 161 | 13 | Table 5 (AE: | AIFA | Please specify better the research question e.g. | We reported the text present in the HTA Rapid Assessment Core Model. |

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| | | *A0006)* | | economic impact, years of life lost etc. | We'll evaluate all available evidence on the burden associated with HCV and this will be clarified. |
| 162 | 13 | Table 5 (AE: *D0006)* | AIFA | In this assessment element the effect on morbidity of different products should be compared not only in relation to the comparators, but also to each other. It is suggested to change the wording of the AE in "How do sofosbuvir+ledipasvir; sofosbuvir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir; simeprevir affect sustained viral response at 12 (or 24 for question b) weeks in relation to the comparators, and one in comparison to each other? The same change should be made for questions c to d. | Agreed. |
| 163 | 14 | Table 5 (AE: *D0012)* | AIFA | In this assessment element the effect on QoL of different products should be compared not only in relation to the comparators, but also to each other. It is suggested to change the wording of the AE in: "What is the effect of sofosbuvir+ledipasvir; sofosbuvir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir; simeprevir on generic health-related quality of life in relation to the comparators and one in comparison to each other? | Agreed. QoL is an important endpoint but is not reported in all studies and data reported will need to be interpreted with care. Same comparisons in principle as for SVR. |
| 164 | 15 | Safety | AIFA | The assessment elements should evaluate not only the safety profile of the technologies in | The Assessment Elements are selected based |

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| | | Domain | | relation to the comparators but also one in comparison to each other. Please modify the wording of AE C0008, C0002, C0004 and B0010 properly. | on the HTA Core Model for rapid REA.<br><br>Some modifications were made; we refer to the table in project plan Appendix. |
| 165 | 16 | Section 4.1 | EFPIA | EFPIA questions whether the comparison between the EUnetHTA report and recent IQWIG assessments will support the laudable goal of "increase the usability and uptake of jointly produced reports", because:<br><br>• The final assessment conducted in Germany is done by the GBA on the basis of an IQWIG report; therefore the IQWIG assessment does not necessarily reflect the final German assessment<br><br>• IQWIG, and subsequently the GBA, review individual products at time of launch, rather than several products after launch<br><br>For the comparison to be relevant, a representative sample of agencies should be looked at, rather than only one country, and should be conducted by a neutral third party.<br><br>The goal of increasing the usability and uptake of jointly produced reports should be incorporated in all pilots, and the comparison foreseen in this pilot could be undertaken with | The importance of conducting a comparison between the EUnetHTA report and recent IQWIG assessments is to support the objective as listed in Article 15 of the Directive on Patients' Rights in Cross-Border Healthcare (Directive 2011/24/EU),under item 3.b:<br><br>To support collaboration between Member States in developing and sharing methodologies for health technology assessment including relative effectiveness assessment;<br><br>The goal here is to compare methodologies in clinical effectiveness assessments, and the methodology of IQWIG, as a leader in clinical effectiveness assessment methodology will be compared to the work of this EUnetHTA REA as a further step in quality control and development of methodology.<br><br>It is not solely about comparing reports or national uptake in this case, but examining methods and conducting a tabular comparison of results. This will be clarified in the project plan. |

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| | | | | already completed assessments (finalized and published pilots). | |
| 166 | 16 | Section 4.1 | JnJ | **Comparison of report with IQWiG Evaluations**<br><br>No explanation has been given as to why only Germany, only 1 of 28 Member States, has been selected for this comparison. For this comparison to be relevant on an EU level, a representative sample of member state reviews should be selected from agencies that have previously undertaken Hep C reviews. Alternatively, this appears as Germany-centric review, looking at the relevance of the EUnetHTA review to the Germany market, and as such should not make up part of the Core report.<br><br>We want to highlight the fact that quite some variation was seen in the assessment of various HCV agents by the EU HTA bodies, despite submission of the same evidence package. This lack of consistency has been pointed out by the French inter-ministry control body IGAS (p197 -)<br><br>http://www.ladocumentationfrancaise.fr/var/storage/rapports-publics/154000078.pdf<br><br>Furthermore, if IQWiG continues to be the only country that the EUnetHTA report is compared | The importance of conducting a comparison between the EUnetHTA report and recent IQWIG assessments is to support the objective as listed in Article 15 of the Directive on Patients' Rights in Cross-Border Healthcare (Directive 2011/24/EU),under item 3.b:<br><br>To support collaboration between Member States in developing and sharing methodologies for health technology assessment including relative effectiveness assessment;<br><br>The goal here is to compare methodologies in clinical effectiveness assessments, and the methodology of IQWIG, as a leader in clinical effectiveness assessment methodology will be compared to the work of this EUnetHTA REA as a further step in quality control and development of methodology.<br><br>It is not solely about comparing reports or national uptake in this case, but examining methods and conducting a tabular comparison of results. This will be clarified in the project plan. |

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| | | | | with, we expect the report to also acknowledge that the IQWiG reports are frequently not endorsed by the local decision-maker (GBA) it was designed to inform, as was the case with some Hep C reports. It will therefore be more informative and reflective of reality to also consider the final GBA assessments when looking at the HTA evaluation in Germany. | |
| 167 | 16 | Line 9 | IHS | Space between HepC | Has been corrected. |
| 168 | 16 | Line 16 | IHS | IQWIQ needs to be changed to IQWIG | Has been corrected. |
| 169 | 16 | Line 23 | IHS | Space between HepC | Has been corrected. |
| 170 | 16 | Section 4.1 | BMS | We question whether the comparison between the EUnetHTA report and recent IQWIG assessments will support the laudable cause of "increase the usability and uptake of jointly produced reports", because:<br>• The final assessment conducted in Germany is done by the GBA on the basis of an IQWIG report; therefore the IQWIG assessment does not necessarily reflect the German assessment<br>• IQWIG and subsequently the GBA review individual products at time of launch, rather | The importance of conducting a comparison between the EUnetHTA report and recent IQWIG assessments is to support the objective as listed in Article 15 of the Directive on Patients' Rights in Cross-Border Healthcare (Directive 2011/24/EU),under item 3.b:<br>To support collaboration between Member States in developing and sharing methodologies for health technology assessment including relative effectiveness assessment;<br>The goal here is to compare methodologies in clinical effectiveness assessments, and the methodology of IQWIG, as a leader in clinical effectiveness assessment methodology will be |

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| | | | | than several products after launch<br><br>To be a relevant comparison a representative sample of agencies should be looked at, rather than only one country. | compared to the work of this EUnetHTA REA as a further step in quality control and development of methodology.<br><br>It is not solely about comparing reports or national uptake in this case, but examining methods and conducting a tabular comparison of results. This will be clarified in the project plan.<br><br>Furthermore, conducting a methodological comparison of IQWIG to a EUnetHTA report allows for further exploration of participation and transferability between EUnetHTA output and national work. Inviting large countries to participate through various activities provides additional information and experience in bringing cohesiveness of EUnetHTA within the different member states. |
| 171 | 16 | Section 4.1. | AIFA | In order to be defined a scientific exercise it should be better explained how the comparison has been chosen (why only IQWIG?). Moreover it should specified that the different timelines of two assessments will be taken into account in the discussion of results of this comparison (e.g. because of the emerging of new evidences). Moreover since it was specified that "This comparison will be an internal process and will not follow the EUnetHTA pilot procedure" this | The importance of conducting a comparison between the EUnetHTA report and recent IQWIG assessments is to support the objective as listed in Article 15 of the Directive on Patients' Rights in Cross-Border Healthcare (Directive 2011/24/EU),under item 3.b:<br><br>To support collaboration between Member States in developing and sharing methodologies for health technology assessment including |

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| | | | | analysis should not be part of the assessment report, but published as a different document. | relative effectiveness assessment;<br><br>The goal here is to compare methodologies in clinical effectiveness assessments, and the methodology of IQWIG, as a leader in clinical effectiveness assessment methodology will be compared to the work of this EUnetHTA REA as a further step in quality control and development of methodology.<br><br>Furthermore, EUnetHTA aims to increase national uptake and promote participation and collaboration among member states. Conducting a methodological comparison of IQWIG to a EUnetHTA report allows for further exploration of participation and transferability between EUnetHTA output and national work. Inviting large countries to participate through various activities provides additional information and experience in bringing cohesiveness of EUnetHTA within the different member states.<br><br>It is a useful exercise, but it is correct that the comparison is an internal process, and will be published as a separate document. |
| 172 | 16 | Section 4.1 | AIFA | Please change IQWIQ with IQWIG. | Has been corrected. |
| 173 | 17 | Table 6 | EFPIA | Ethical, organizational, social and legal aspects are context specific and therefore out of scope of | These domains are indeed country specific, and will therefore not be assessed in depth in this |

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| | | | | any European activity. | study. However, we will use the checklist to identify possible important topics to be investigated on a national level if deemed necessary by national HTA organizations. |
| 174 | 17 | Table 6 | EFPIA | "Potential non-use of new compounds due the high price may also be a potential aspect in general population and in particular for PWIDs in some countries". In addition to questioning the relevance of assessing ethical issues at the European level, EFPIA questions the relevance of this item under "ethical issues". Pricing is the result (output) of a national pricing and reimbursement process and can therefore not be considered as an input problem into the system. | It is not currently within the remit of a EUnetHTA WP5 rapid REA to assess pricing or ethical issues at the European level. The checklist serves as a tool to notify local assessors of potential issues that may be relevant to the national setting. Therefore the relevance of this potential issue is to be decided upon and subsequently assessed at the national/local level. |
| 175 | 17 | Table 6 | BMS | Ethical, organizational, social and legal aspects are context specific and should therefore be out of scope of any European assessment. | These domains are indeed country specific, and will therefore not be assessed in depth in this study. However, we will use the checklist to identify possible important topics to be investigated on a national level if deemed necessary by national HTA organizations. |
| 176 | 17 | Section 4.2 | BMS | The section of Table 6 on Ethical aspects states: "potential non-use of new compounds due the high price may also be a potential aspect in general population and in particular for PWIDs in some countries". This suggests that pricing may be a subject of this assessment which would be | The assessment will not regard the pricing decision but it's implications without referring to a specific country. |

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| | | | | inappropriate | |
| 177 | 17 | Section 4.2 | Lazio | The impact of different national pricing and/or reimbursement schemes (e.g. undisclosed conditional agreements vs disclosed ones; covered discount) on drug(s) access should be part of this EUnetHTA REA. | The assessment will not regard the pricing decision but it's implications without referring to a specific country. |
| 178 | 18 | Legal Section | IHS | There may be some legal ramifications. In some countries patients with haemophilia have been infected through state products and there may be a legal precedent to treat these patients. This may arise more so in relation to patients who are SVR positive but do not fulfill the criteria under current treatment guidelines for cirrhosis or fibrosis. Although I am unsure if this is within the scope of the REA | This is indeed out of the scope of the EUnetHTA REA. |
| 179 | 18 | Section 4.2 | Lazio | Table 3, section 4, question 4.1. The impact of the introduction of new medicine and its nonuse on the increasing legal actions (by patients/clinicians) should be part of this EUnetHTA REA | Thank you for this suggestion. Although relevant, we think that this is outside of the scope of REA. |
| 180 | 19 | 5.1 Milestones and Deliverables | IQWIG | The timeslot for the assessment phase starts at the deadline for comments of the project plan and ends shortly after the finalisation of the project plan. While it seems reasonable to start the assessment early, we would suggest foreseeing enough time to adjust the | After discussion with the authors, small adaptations to the timelines have been made. Given the size of the authoring team, and the aimed timeliness of this assessment, these timelines are feasible. |

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| | | | | assessment after the finalisation of the project plan.<br><br>The timelines for the assessment phase seem very ambitious. The time planned for the preparation of the first draft assessment for review by the dedicated reviewers would even be very ambitious for a usual REA including one drug. It seems unrealistic for the assessment under discussion which not only includes a number of drugs, but also a large number of relevant scenarios and is planning for indirect comparisons and the inclusion of single arm trials. | |
| 181 | 19 | Table 7 | MSD | Suggest to allow public comments/stakeholder engagement in the "decision upon scope of NMA". | Given the independent nature of this EUnetHTA assessment, this decision will be made by the EUnetHTA team. |
| 182 | 20 | Communication | IQWIG | In Table 8 (Communication), we suggest to send the final project plan to the dedicated reviewers immediately after its finalization on August 14, including replies to comments. | Since the timelines have been adapted, the final project plan will be available on September 1. It will be published on the EUnetHTA website, this way the dedicated reviewers can take this into account when reviewing the first draft of the assessment report. |