KCE-Belgium	AAZ-Croatia	A. Gemelli-Italy	HVB-Austria	RIZIV/INAMI-Belgium

EUnetHTA rapid Relative Effectiveness Assessment

Project ID: WP5-SA-6

Rapid Relative Effectiveness Assessment of new pharmaceuticals for the treatment of chronic hepatitis C

Project description and planning

Authors

Belgian Health Care Knowledge Center (KCE), Belgium
Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ), Croatia
Università Cattolica del Sacro Cuore, Policlinico Agostino Gemelli, Italy
National institute for health and disability insurance (RIZIV-INAMI), Belgium
Hauptverband der österreichischen Sozialversicherungsträger (HVB), Austria

Contents:

A. VERSION LOG

Version number	Date	Involvement	Modification	Reason for the modification
V1	28/05/2015	All Authors + Coordination team	Authoring team created first draft	First draft of the project Plan
V2	23/06/2015	All Authors + Coordination team	First draft has been updated after discussion with all Authors	Project Plan will go to public consultation
V3	01/09/2015	All Authors + Coordination team	Final draft has been created based on the comments received during the public consultation	Comments received during public consultation

B. PROJECT PLAN

1.0 PARTICIPANTS

Table 1. Project participants

#	Agency	Country	Role in the project	Distribution of work
1	KCE	Belgium	Author	Coordination of Clinical Effectiveness / Safety Domains / NMA
2	AAZ	Croatia	Author	Description and technical characteristics of the technology / Clinical Effectiveness / Safety Domains
3	A. Gemelli	Italy	Author	Health Problem and Current Use of Technology Domain
4	RIZIV	Belgium	Author	Comparison with IQWiG reports
5	HVB	Austria	Co-Author	Co-author in all domains, focus on Clinical Effectiveness / Safety Domains; Support in IQWiG comparison
6	FIMEA	Finland	Dedicated reviewer	Review of project plan and first assessment
7	IQWiG	Germany	Dedicated reviewer	Review of project plan and first assessment
8	AETSA	Spain	Dedicated reviewer	Review of project plan and first assessment
9	HAS	France	Dedicated reviewer	Review of project plan and first assessment
10	NOKC	Norway	Dedicated reviewer	Review of project plan and first assessment
11	MoH Slovakia	Slovakia	Dedicated reviewer	Review of project plan and first assessment
12	AIFA	Italy	Dedicated reviewer	Review of project plan and first assessment
13	SNHTA	Switzerland	Dedicated reviewer	Review of project plan and first assessment
14	SAGEM HTA	Turkey	Dedicated reviewer	Review of project plan and first assessment
15	MoH Malta	Malta	Dedicated reviewer	Review of project plan and first assessment
16	NHS Latvia	Latvia	Dedicated reviewer	Review of project plan and first assessment

17	ZIN	The Netherlands	Dedicated reviewer	Review of project plan and first assessment
18	Medical Writing Services	UK	Editor / Medical writer	Editorial Review of the First Assessment
19	ZIN	The Netherlands	Project coordinator	Coordination between involved parties throughout the pilot duration

1.1 PROJECT STAKEHOLDERS

Table 2. Project stakeholders

Organization	Type of organization
Gilead	Market Authorization Holder of Sofusbuvir, Sofusbuvir+Ledipasvir
Abbvie	Market Authorization Holder of Ombitasvir + Paritaprevir + Ritonavir, Dasabuvir
Johnson & Johnson	Market Authorization Holder of Simeprevir
Bristol-Myers-Squibb	Market Authorization Holder of Daclatasvir
European Liver Patients Association	Patient Organisation
Irish Haemophilia Society	Patient Organisation
European Association for the Study of the Liver	Physician Organisation

2.0 PROJECT INTRODUCTION/ RATIONALE

Project introduction/ rationale
The rationale for this pilot assessment report is to test the capacity of national or regional HTA bodies to collaboratively produce structured rapid core HTA information. In addition, the application (transferability) of those collaboratively produced HTAs in the national or regional contexts will be tested. Recently, we have noticed that there has been a great deal of interest in the new Hepatitis C treatments that have acquired market authorization in Europe. These treatments (single but also combination treatments) may provide an opportunity for many patients to be treated. In 2014, EUnetHTA was asked by DG SANTE (the Directorate General for Health and Food Safety) to provide an overview of national HTA assessments of sofosbuvir in order to assist the Member States in their discussions on the reimbursement and pricing of this specific compound. At the end of 2014, our WP5 members indicated within our independent topic selection and prioritisation procedure that a joint REA of the new treatment options for Hepatitis C would be of high relevance and interest across Europe. As a result, it was decided in WP5 of EUnetHTA to address this need and to initiate a joint rapid REA of this new treatment options for Hepatitis C.

3.0 PROJECT SCOPE AND OBJECTIVES

	List of project objectives	Indicator (and target)
1.	To test the capacity of national or regional HTA bodies to collaboratively produce structured rapid core HTA	Production of 1 pilot rapid assessment
2.	To test the application of these collaboratively produced rapid assessments into local (e.g. regional or national) context	Production of ≥1 local (e.g. national or regional) report per pilot rapid assessment

In this assessment we will primarily focus on the assessment of these recently authorized treatment options: 1) sofosbuvir; 2) simeprevir; 3) daclatasvir; 4) sofosbuvir and ledipasvir; 5) ombitasvir, paritaprevir, ritonavir; with or without 6) dasabuvir and/or combinations of these products. During the pilot we will compare these new treatment options to the options that are longer on the market but will also aim to compare these treatment combinations to each other by using indirect comparison methods such as Network Meta analysis (NMA). Depending on the compound, the analysis will be done for specific genotypes and patient populations, with relevant comparators.

Table 3. Project Scope: PICO (please see HTA Core Model for Rapid REA of pharmaceuticals)

Description	Project scope
Population	**Health conditions:** Chronic hepatitis C **ICD-10 code:** B18.2 Chronic hepatitis C **MeSH-terms***: "Hepatitis C, Chronic" [*C02.440.440.120, C02.782.350.350.120, C06.552.380.350.120, C06.552.380.705.440.120] • Adults ≥ 18 yrs with genotype 1, 2, 3, 4, 5 and 6 chronic hepatitis C • Patients who have not been previously treated (treatment-naïve) • Patients who have previously been treated (treatment-experienced) • No limitations in terms of fibrosis and/or compensated/decompensated cirrhosis and/or hepatocellular carcinoma and/or other concomitant clinical condition(s) (see subgroup analysis section)
Interventions	**Possible new treatments (by HCV genotype) and their possible comparators are listed in a separate table in annex.** 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. **sofosbuvir (SOVALDI®)** Sofosbuvir is a uridine nucleotide analogue that inhibits HCV nonstructural protein (NS) 5B RNA-dependent RNA polymerase, preventing viral replication. Genotypes: 1 to 6. Sofosbuvir is administered orally. *ATC code: J05AX15* *MeSH-term for intervention: "sofosbuvir" [C553296]*

	sofosbuvir + ledipasvir (HARVONI®) Sofosbuvir+ledipasvir is a fixed-dose combination product. Sofosbuvir is a uridine nucleotide analogue that inhibits HCV NS5B RNA-dependent RNA polymerase, and ledipasvir is a macrocyclic antiviral agent and an inhibitor of the HCV NS5A protein. They both act to inhibit viral replication. Genotypes: 1, 3 and 4. HARVONI (sofosbuvir-ledipasvir) is administered orally. *ATC code: J05AX65* *MeSH-term for intervention: "ledipasvir, sofosbuvir drug combination" [C000595958]* **ombitasvir + paritaprevir + ritonavir (VIEKIRAX®)** Ombitasvir + paritaprevir + ritonavir is a fixed dose combination product. Ombitasvir is an inhibitor of HCV NS5A, which plays a role in viral genome replication, virus assembly, and modulation of host pathways. Paritaprevir is an inhibitor of NS3/4A serine protease which cleaves viral polyprotein after translation. Ritonavir is a cytochrome P450 (CYP) 3A4 inhibitor that increases the systemic exposure of the CYP3A4 substrate paritaprevir. Genotypes: 1 and 4. VIEKIRAX is administered orally. *ATC code: J05AX67* *MeSH-term for intervention: "ABT-267" (ombitasvir) [C586094], "ABT-450" (paritaprevir)[C585405],"ritonavir" [D019438, D02.886.675.653, D03.383.129.708.653]* **dasabuvir (EXVIERA®)** Dasabuvir is a non-nucleoside inhibitor of HCV NS5BRNA-dependent RNA polymerase that has a role in viral genome replication, used in combination with other medicines for treatment of CHC (ombitasvir/ paritaprevir /ritonavir, with or without ribavirin). Genotype: 1. Dasabuvir is administered orally. *ATC code: J05AX16* *MeSH-term for intervention: "ABT-333" [C588260]* **simeprevir (OLYSIO®)** Simeprevir is a protease inhibitor. It inhibits the NS3/4A enzyme that is essential for HCV replication and therefore prevents viral replication. Used in combination with other medicines for treatment of CHC /peginterferon alfa + ribavirin or sofosbuvir (+/- ribavirin)/. Genotypes: 1 and 4. Simeprevir is administered orally. *ATC code: J05AE14* *MeSH-term for intervention:"simeprevir" [C532453]* **daclatasvir (DAKLINZA)** Daclatasvir is an inhibitor of NS5A, a multifunctional phosphoprotein, which plays a role in HCV replication. Used in combination with other medicines for treatment of CHC /sofosbuvir (with or without ribavirin) or with peginterferon alfa and ribavirin/. Genotypes: 1, 3 and 4. Daclatasvir is administered orally. *ATC code: J05AX14* *MeSH-term for intervention: "BMS-790052" [C549273]*
Comparison	Active comparators include combinations based on: **peginterferon alfa-2a (PEGASYS®)/peginterferon alfa-2b (PEGINTRON®, VIRAFERONPEG®)** Peginterferon alfa plays a major role in the non-specific antiviral response through a variety of actions, eg antiviral, immunomodulatory, cytostatic, and antitumor. Peginterferon alfa is administered subcutaneously, for genotypes 1 to 6. (ATC code: L03AB11, *MeSH-term: "peginterferon alfa-2a"* [*C100416]; "peginterferon alfa-2b [C417083]")*, Peginterferon alfa is often used in combination with ribavirin.

	ribavirin (REBETOL®, RIBAVIRIN MYLAN®, RIBAVIRIN TEVA®) Ribavirin is a nucleoside analogue that is thought to interfere with the production or action of viral DNA and RNA. Ribavirin is used orally and in combination with other medicines for treatment of CHC (peginterferon alfa-2b or interferon alfa-2b for genotypes 1 to 6 or in combination with boceprevir and peginterferon alfa-2b for genotypes 1). (ATC code: J05AB04, *MeSH-term: "ribavirin" [D012254]).* **telaprevir (INCIVO®)** Telaprevir is a protease inhibitor. It inhibits the NS3/4A enzyme that is essential for HCV replication and therefore prevents viral replication. Telaprevir is administered orally, in combination with peginterferon alfa and ribavirin (for genotype 1 only). (ATC code: J05AE11, *MeSH-term: "telaprevir" [C486464])*. **boceprevir (VICTRELIS®)** Boceprevir is a protease inhibitor. It inhibits the HCV NS3 enzyme that is essential for HCV replication and therefore prevents viral replication. Boceprevir is administered orally, in combination with peginterferon alfa and ribavirin (for genotype 1 only). (ATC code: J05AE12 ,*MeSH-term:" N-(3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl)-3-(2-((((1,1-dimethylethyl)amino)carbonyl)amino)-3,3-dimethyl-1-oxobutyl)-6,6-dimethyl-3-azabicyclo(3.1.0)hexan-2-carboxamide" [C512204])*. **See Interventions** **Rationale:** ***1.*** Comparators evaluated in the clinical trials for different interventions under evaluation, EPAR SPC, clinical guidelines and EUnetHTA guideline on most appropriate comparator(s) [1,2], please see Appendix 1; ***2.*** The aim of the pilot is to compare new oral direct acting antivirals.
Outcomes	**Outcomes for effectiveness:** • Sustained Virological Response 12 weeks after end of treatment – SVR12 • Sustained Virological Response 24 weeks after end of treatment – SVR24 Withdrawals before first treatment are relevant as this may be higher if randomized to IFN containing arm in open label RCT • Development of resistance (and transmission of resistant strains) • Relapse rate after SVR12/24 • Progression of liver fibrosis • Incidence of decompensated liver disease and HCC (and the associated need for liver transplantation) • Health-related quality of life

	• Mortality **Outcomes for safety:** • Adverse events (AEs) of treatment (Any AEs, discontinuation due to AE, Serious AE (SAE), Death as SAE, most frequent AE) Drug-drug interactions will be discussed if these result in AEs. Rationale for choosing the outcomes: Commonly used outcomes in clinical studies on hepatitis C, clinical guidelines and outcomes important for REA; based on recommendations from the EUnetHTA methods guideline on clinical and surrogate endpoints and safety [3-5].
Subgroups analysis **(If possible with available data)**	• Treatment naïve or non-responder to previous treatment • Baseline fibrosis stage e.g. presence or absence of cirrhosis • Baseline HCV RNA • Presence or absence of HIV coinfection • Presence or absence of HBV coinfection • Patients intolerant to or ineligible for interferon treatment • Patients treated pre- and post-liver transplantation • Presence or absence of IL28b polymorphism (in IFN-based regimens) • Presence or absence of baseline resistance (Ns5A, Ns3) • Geno-subtype (G1a, G1B, G4, ...)
Study design	• Randomized controlled trials • Non-randomized controlled trials • Prospective observational studies • Prospective uncontrolled trials

4.0 PROJECT APPROACH AND METHOD

Table 4a. Project approach and method

Project approach and method
Questions from the domains *Description and technical characteristics of the technology* and *Health Problem and Current Use of Technology* will be answered by the EPAR and Summary of Product Characteristics and basic literatures identified through the systematic literature search, including clinical guidelines. No quality assessment tool will be used for the domains *Description and Technical Characteristics of the Technology* and *Health Problem and Current Use of Technology*, but multiple sources will be used in order to validate individual, possibly biased, sources. Descriptive analysis will be performed on

different information sources.

A systematic literature search (not limited by publication date) will be performed according to the EUnetHTA guideline on Information retrieval [EUnetHTA 2015], on standard medical and HTA databases,

Citation:

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

Specifically, the following databases will be searched: MEDLINE accessed through OVID or Pubmed; EMBASE; and Cochrane Library searching the following databases: The Cochrane Central Register of Controlled Trials (CENTRAL), The Cochrane Database of Systematic Reviews (Cochrane Reviews), The Database of Abstracts of Reviews of Effects (DARE) and The Health Technology Assessment Database (HTA). Also regulatory websites will be searched eg EPAR.

In addition, the following clinical trials registries will be assessed, *for registered* ***completed,*** *ongoing* ***and withdrawn*** *clinical trials or results posted through the* WHO International Clinical Trials Registry Platform (ICTRP).

The MAH will be contacted to obtain study reports for those studies without results reported as full publication.

Relevant references identified using the literature search (after duplicates were removed) will be screened and assessed for eligibility independently by two reviewers. The reference lists of relevant systematic reviews and health technology assessment reports will be checked for other relevant studies also.

Differences in selection results will be discussed in order to achieve consensus; a third reviewer will be involved in case of uncertainty. The study selection process will be presented according to the PRISMA flowchart.

In case that a recent, high quality (and appropriate for our PICO) systematic review (SR) is found, update of this SR will be done with new RCTs [22, 23]. The quality of the included systematic review will be assessed using AMSTAR [7].

Data extraction will be performed by one reviewer on pre-defined extraction tables and double-checked regarding completeness and accuracy by a second reviewer. Any differences in extraction results will be discussed to achieve consensus; a third reviewer will be involved in case of uncertainty.

The study types included in the clinical effectiveness and safety domains will focus on randomised controlled trials, non-randomised 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.

In addition to the comparators listed above against which benefits and harms of the interventions will be assessed, studies covering any other comparator (including placebo) will be used for indirect comparisons, as appropriate.

Additional information on the use and effectiveness and safety of these therapies and their comparators in real world from for instance pragmatic and observational studies may be discussed additionally if the available data are relevant and of sufficient quality.

Risk of bias will be evaluated independently by two reviewers using the Cochrane risk of bias checklist and EUnetHTA methods guidelines on internal validity of RCTs and non-randomised studies on interventions for studies which forms the basis for the direct evidence. [6,8,9]

When the primary studies are assessed and summarized, the possibilities to combine the studies using direct (meta-analysis) and indirect comparison methods, including network meta-analysis (NMA), will be assessed. Elements that will be taken into account are; type of studies, 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. For NMA, preference will be given to Bayesian hierarchical modelling using Gibbs sampling [10]. When only a part of the studies can be integrated into a network or into a number of separate networks, due to lack of common comparators or the presence and dominance of single arm studies, added value of doing this will first be discussed. 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 [6]. No indirect comparison methods that require the use of individual patient data will be used.

Direct evidence related to efficacy and safety will be assessed by using the GRADE-methodology [11]. The EUnetHTA methods guideline on direct and indirect comparisons together with suggestions from the GRADE Working Group on how to rate the quality of the evidence from network meta-analysis will be used for indirect evidence analysis [12, 13].

Table 4b. Preliminary Evidence

Preliminary evidence table
The extraction of information from included **primary studies** will follow the data extraction template that can be found in the appendix.
Outcomes
Efficacy • Sustained Virological Response 12 weeks after end of treatment – SVR12 • Sustained Virological Response 24 weeks after end of treatment – SVR24 • Development of resistance (and transmission of resistant strains) • Relapse after SVR12/24 • Progression of liver fibrosis • Incidence of decompensated liver disease and HCC (and the associated need for liver transplantation) • Health-related quality of life • Mortality
Safety • Adverse events (AEs) of treatment (any AEs, discontinuation due to AE, Serious AE (SAE), death as SAE, most frequent AE) • Drug-drug interactions will be discussed if these result in AEs.

Selected assessment elements

The table shows the assessment elements and the translated research questions that will be addressed in the assessment. They are based on the assessments elements contained in the document “Model for Rapid Relative Effectiveness Assessment”.

Table 5. Assessment elements and translating research questions

ID	Topic	Topic Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of ‘Critical’ elements
Description and technical characteristics of technology				
B0001 Mandatory element	Features of the technology and comparators	What is the technology and the comparator(s)?	Yes	What are sofosbuvir+ledipasvir; sofosbuvir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir; simeprevir and the comparators?
A0020 Mandatory element	Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?	Yes	For which indications have sofosbuvir+ledipasvir; sofosbuvir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir; simeprevir received marketing authorisation?
B0002 Mandatory element	Features of the technology and comparators	What is the claimed benefit of the technology in relation to the comparators?	Yes	What is the claimed benefit of sofosbuvir+ledipasvir; sofosbuvir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir; simeprevir in relation to the comparators and one in comparison to each other?
B0003 *Non-Mandatory element*	*Features of the technology*	*What is the phase of development and implementation of the technology and the comparator(s)?*	No	/
B0004 *Non-Mandatory element*	*Features of the technology*	*Who administers the technology and the comparators and in what context and level of care are they provided?*	Yes	Who administers sofosbuvir+ledipasvir; sofosbuvir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir; simeprevir and the comparators and in what context and level of care are they provided?
B0008 *Non-Mandatory element*	*Investments and tools required to use the technology*	*What kind of special premises are needed for the technology and the comparator (s)?*	Yes	What kind of special premises are needed for sofosbuvir+ledipasvir; sofosbuvir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir; simeprevir and the comparators?
B0009	*Investments and tools*	*What supplies are needed for the*	No	/

ID	Topic	Topic Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'Critical' elements
Non-Mandatory element	*required to use the technology*	*technology and the comparator (s)?*		
A0021 *Non-Mandatory element*	*Regulatory Status*	*What is the reimbursement status of the technology?*	Yes	What is the reimbursement status of sofosbuvir+ledipasvir; sofosbuvir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir; simeprevir?
Health problem and current use of technology				
A0002 Mandatory element	Target Condition	What is the disease or health condition in the scope of this assessment?	Yes	a) What is the disease or health condition in the scope of this assessment? b) What are the incidence and prevalence of the HCV? Figures in EU if possible per genotype, age group, figures per country. c) What is the mortality due to HCV and its complications?
A0003 *Non-Mandatory element*	Target Condition	*What are the known risk factors for the condition?*	Yes	a) What are the known risk factors for the chronic hepatitis C? b) What are the known risk factors for progression of liver fibrosis? c) What are the known risk factors for decompensated cirrhosis? d) What are the known risk factors for hepatocellular carcinoma?
A0004 *Non-Mandatory element*	Target Condition	What is the natural course of the disease or health condition?	Yes	What is the natural course of the condition?
A0005 Mandatory element	Target Condition	What are the symptoms and the burden of disease or health condition for the patient?	Yes	a) What are the symptoms and the burden of disease for the patient? b) What is the mortality and/or hospitalization degree caused by the disease?
A0006 *Non-*	Target Condition	*What is the burden of disease for*	Yes	What is the burden of the disease for society?

ID	Topic	Topic Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'Critical' elements
Mandatory element		*society?*		
A0024 *Non-Mandatory element*	Current Management of the Condition	*How is the disease or health condition currently diagnosed according to published guidelines and in practice?*	Yes	How is the health condition currently diagnosed according to published European guidelines and in practice?
A0025 Mandatory element	Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	Yes	How is the disease or health condition currently managed according to published European guidelines and in practice?
A0007 Mandatory element	Target Population	What is the target population in this assessment?	Yes	What is the target population in this assessment?
A0023 Mandatory element	Target Population	How many people belong to the target population?	Yes	How many people belong to the target population? Specify, if possible, for each genotype.
A0011 *Non-Mandatory element*	Utilisation	*How much are the technologies utilised?*	Yes	How much are the technologies and their comparators utilised?
Clinical effectiveness				
D0001 Mandatory element	Mortality	What is the expected beneficial effect of the intervention on mortality ?	Yes	Indirect modeling is required for the evaluation of the effect on mortality (not planned in this project).
D0003 *Non-Mandatory element*	*Mortality*	*What is the effect of the technology on the mortality due to causes other than the target disease?*	Yes	/
D0005 Mandatory element	Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the	Yes	Literature will be searched for effect of SVR on disease progression (fibrosis, HCC).

ID	Topic	Topic Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'Critical' elements
		disease or health condition or disease?		
D0006 Mandatory element	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	Yes	a) How do the new treatments (see Appendix 1) affect sustained viral response at 12 weeks in relation to the comparators? b) How do the new treatments (see Appendix 1) affect sustained viral response at 24 weeks in relation to the comparators? d) How do the new treatments (see Appendix 1) affect the development of resistant strains in relation to the comparators? e) How do the new treatments (see Appendix 1) affect the relapse rate in relation to the comparators? f) How do the new treatments (see Appendix 1) affect the long term outcomes (decompensated liver disease, HCC, death) in relation to the comparators?
D0011 *Non-Mandatory element*	*Function*	*What is the effect of the technology on patients' body functions?*	No	/
D0016 *Non-Mandatory element*	*Function*	*How does the use of technology affect activities of daily living?*	No	/
D0012 Mandatory element	Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	Yes	How do the new treatments (refer to table) affect the generic quality of life in relation to the comparators?
D0013 Mandatory element	Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	Yes	How do the new treatments (refer to table) affect the disease specific quality of life in relation to the comparators?
D0017	*Patient satisfaction*	*Was the use of the technology*	No	/

ID	Topic	Topic Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'Critical' elements
Non-Mandatory element		*worthwhile?*		
Safety				
C0008 Mandatory element	Patient safety	How safe is the technology in relation to (the) comparator(s)?	Yes	a) How do the new treatments (refer to table) affect the frequency and type of adverse events in relation to the comparators? b) How do the new treatments (refer to table) affect the frequency and type of serious adverse events in relation to the comparators?
C0002 *Non-Mandatory element*	*Patient safety*	*Are the harms related to dosage or frequency of applying the technology?*	Yes	Are the harms related to dosage or frequency or administration of the new treatments in relation to the comparators?
C0004 *Non-Mandatory element*	*Patient safety*	*How does the frequency or severity of harms change over time or in different settings?*	Yes	How does the frequency or severity of harms changes over time or in different settings of the new treatments in relation to the comparators?
C0005 Mandatory element	Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	Yes	What are the susceptible patient groups that are more likely to be harmed with the new treatments in relation to the comparators?
C0007 *Non-Mandatory element*	*Patient safety*	*Are the technology and comparator(s) associated with user-dependent harms?*	No	/
B0010 *Non-Mandatory element*	*Investments and tools required to use the technology*	*What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?*	Yes	What kind of data/records and/or registry is needed to monitor the use of the new treatments and the comparators?

4.1 COMPARISON OF (TO BE PRODUCED) EUNETHTA REPORT WITH IQWIG EVALUATIONS

One of the goals of EUnetHTA WP5 is to increase the usability and uptake of jointly produced reports. In order to achieve this, information on the different procedures and ways of assessment within Europe can provide valuable input.

Therefore, a scientific exercise will be undertaken, related to the review of the Hep C compounds. This comparison will focus on the following research issues, taking into account the different timelines of the assessments in the discussion section:

1.) Verification of comparator(s) used for each antiviral treatment (sofosbuvir+ledipasvir; sofosbuvir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir; simeprevir) given to various patient groups (i.e. according to genotype, previous treatment, comorbidities, etc.) as it was studied in this EUnetHTA rapid relative assessment and several recent IQWIG assessment reports.

In case of match of the same comparator(s) used in the same patient group in both IQWiG report and EUnetHTA report:
2.) Tabular comparison of results of EUnetHTA rapid REA and IQWIG reports for each match.
3.) Check to what extent the assessment was similar or different based on the PICO question, information retrieval, literature selection, and quality assessment of studies.

This comparison will start when the second draft of the rapid REA on the Hep C compounds is finalized. Timelines are set parallel to the production of the rapid REA and will highly depend on the timely production of the rapid REA report. This comparison will be an internal process and will not follow the EUnetHTA pilot procedure. Next to the main responsible, the Authors and the Co-Author (See Table 1.), IQWIG will have a role as reviewer and will be involved in all relevant steps. The resulting report will be publicly available, and might lead to a scientific publication.

4.2 CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, SOCIAL AND LEGAL ASPECTS

The following checklist is a short list of questions in order to determine whether there are specific ethical, organisational, social and legal aspects which also need to be addressed. Since the assessment is comparative in nature, only new issues should be dealt with, which arise from a difference between the medicine to be assessed and its major comparator(s). Already known problems/issues with regard to ethical, organisational, social and legal aspects which are common to the technology to be assessed and its comparator(s) will, as a rule, not be addressed, as it is not to be expected that the addition of a new medicine will lead to changes.
If a question is answered with ‘yes’, further analysis of these issues may be warranted. If they are answered with no, the domains need not be dealt with further. Examples are provided for clarification (for more details please see also Model for rapid REA:
http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals_final_20130311_reduced.pdf

Table 6. Checklist for potential ethical, organizational, social and legal aspects

This checklist will assess whether the domains not included in a rapid REA (i.e. the ethical, organizational, social and legal domains) could be relevant for the topic of this pilot. If deemed appropriate, the users of the final report can address these issues on a national level. 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. However, the suggested assessment elements will not be answered within this report.

1. Ethical	
1.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	Yes
1.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be ethically relevant?	Yes
Various issues similar to those seen when ARV was introduced for HIV may emerge [14]. For example, effective and safe treatment of hepatitis C in people who inject drugs (PWIDs) may be regarded as a new way of prevention of disease spread, i.e. treatment as prevention [14-16]. 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. EASL 2015 guidelines provide a list stating populations which should be prioritized [17]. Although they give individuals at risk of transmitting HCV a priority, guidance in individual European countries is not always clear [18]. Further subpopulation to take into account is people in prisons [19]. Relevant questions: F0003 Are there any other hidden or unintended consequences of the technology and its applications for patients/users, relatives,other patients, organisations, commercial entities, society, etc.? F0012 How does implementation or withdrawal of the technology affect the distribution of health care resources? F0013 How are technologies with similar ethical issues treated in the health care system? H0012 Are there factors that could prevent a group or person from gaining access to the technology?	
2. Organisational	
2.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparators require organisational changes?	Yes
2.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be organisationally relevant?	Yes
More effective and safe treatments, together with possible increase in public awareness may lead to identification of a greater proportion people who are currently asymptomatic and undiagnosed, leading to an increase in patient flow. The cascade of care for people who were screened positive for hepatitis C, although still not fully conceptualised, includes '1. obtaining HCV screening results; 2. being linked to	

HCV care; 3. receiving diagnostic test results; 4. deciding on and initiating HCV therapy; 5. adhering to and completing HCV therapy' [20]. Clinical and individual level barriers to HCV treatment among general population may emerge, and also among some subpopulations, which may need additional multidisciplinary care, for example PWID or patients on haemodialysis [17, 21].

Relevant questions:

G0001 How does the technology affect the current work processes?

G0100 What kind of patient/participant flow is associated with the new technology?

G0004 What kind of cooperation and communication of activities have to be mobilised?

G0101 What are the processes ensuring access to care of the new technology for patients/participants?

G0009 Who decides which people are eligible for the technology and on what basis?

3. Social	
3.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be socially relevant?	Yes

There is still low awareness of the disease in general population, as well as misconceptions about treatment possibilities, which prevents people to get tested. On the other hand, patients aware of their status who have deferred treatment for various reasons, in particular because of side effects, may wish to take it now. Fewer side effects may result in patients being able to go to work during treatment, which may have an impact at societal level. Social factors and support seem to be very important for PWIDs [21].

Relevant questions:

H0003 What kind of support and resources are needed for the patient or citizen as the technology is introduced?

H0006 How do patients, citizens and the important others using the technology react and act upon the technology?

H0011 What kinds of reactions and consequences can the introduction of the technology cause at

the overall societal level?

H0009 What influences patients' or citizens' decisions to use the technology?

4. Legal	
4.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be legally relevant?	No

5.0 ORGANISATION OF THE WORK

5.1 MILESTONES AND DELIVERABLE(S)

Table 7. Milestones and Deliverables

Milestones/Deliverables	**Start date**	**End date**
Project duration	**18/02/2015**	**15/12/2015**
Pilot Team building (including Workplan)	Feb	March
Contact MAH + Stakeholders: inform and request information	Mid April	
Scoping phase duration		
Receive information from MAH + Stakeholders	Mid April	End of May
Draft Project Plan including scoping document	April	17 June
Public consultation of Project Plan	23 June	7 July
Finalisation Project Plan + Replies to comments	7 July	1 Sept
Assessment phase	**July**	**Dec**
First draft of the pilot assessment	7 July	7 Sept
Review of the first draft of the pilot assessment by dedicated reviewers	8 Sept	21 Sept
Second draft of the pilot assessment	21 Sept	2 Oct
*Start of comparison with IQWiG reports**	*2 Oct*	
Editorial version of the second draft	2 Oct	13 Oct
Public consultation of the editorial version of the pilot assessment	14 Oct	2 Nov
Final version of the pilot assessment	3 Nov	20 Nov
Final technical editing and publication	23 Nov	30 Nov
Local Reports (if applicable)		
Local (national or regional) REA N°1		

Local (national or regional) REA N°2		

*The detailed timelines regarding the IQWiG comparison are as of yet tentative (and dependent on the final timelines of the rapid REA) and thus not included in this draft Project Plan.

5.2 MEETINGS

Due to the amount of stakeholders involved, no face-to-face meeting will be organized. All known and relevant stakeholders are contacted to inform them about this pilot. Simultaneously, they are invited to provide additional data, and to provide feedback in both the public consultation of the project plan and the public consultation of the second draft of the assessment report (see section 7.0).
Within the authoring group, several e-meetings and telephone conferences are scheduled by the pilot coordination team, if considered necessary (see table 8).

6.0 COMMUNICATION

Table 8. Communication

Communication Type	Description	Date	Format	Participants/ Distribution
Scoping	To discuss and reach consensus on the workplan	[18/02/2015]	E-meeting/ teleconference	Author(s), co-author(s), CT
		[19/03/2015]	E-meeting/ teleconference	
	Contact MAH Contact patient groups Contact physician group	[20/04/2015]	Letter	MAH, author(s), co-author(s), CT
	Receive information and response from MAH and stakeholders	[29/05/2015]	E-mail / E-meeting	Author(s), co-author(s), CT
Project Plan with timelines	Information on the timelines, scoping, methods and assessment elements chosen	[01/04/2015] - [10/06/2015]	E-mail / Teleconference	Author(s), co-author(s), CT
	Public consultation of project plan	[18/06/2015] - [02/07/2015]	E-mail	All stakeholders, WP5 Strand A members
First draft of the pilot assessment	To be reviewed by dedicated reviewers	[02/09/2015] – [11/09/2015]	E-mail	Dedicated reviewers
Editorial version of the pilot assessment	Public consultation	[15/10/2015] – [02/11/2015]	E-mail	All stakeholders, WP5 Strand A members
	To discuss comments of consultation (optional)		E-meeting/ teleconference (optional)	Author(s), (dedicated reviewers)

6.1 DISSEMINATION PLAN

The final pilot rapid assessment will be distributed as laid-out in the Work Plan of WP5.
The scientific exercise regarding the comparison with IQWiG results will be published as an addendum, and might lead to a scientific publication.

7.0 COLLABORATION WITH STAKEHOLDERS

Collaboration with Market Authorization Holder (MAH)

The relevant Manufacturers have been notified of our assessment and invited to participate in this pilot.

- MAH has the possibility to provide the complete set of additional clinical effectiveness data on the assessed compounds that has not already been published in the EPAR and/or peer-reviewed international literature.
- Additionally, MAH has the opportunity to provide input during the public consultation of the project plan of the assessment in the second half of June 2015.
- The MAH is asked to provide an expert who can be a point of contact to the authors and answer questions throughout the assessment.
- Finally, MAH will have the opportunity to provide input during the public consultation of the assessment report. The input will be specifically addressed on the comment level during the preparation of the final version of the assessment. The phase of public consultation is estimated to occur in October 2015.

Collaboration with other stakeholders

Several other organizations have been identified as stakeholders in this process. In this case this refers to ELPA (European Liver Patients Organisation), the Irish Haemophilia Society, and the European Association for the Study of the Liver. Those have been contacted in the same way as the MAHs, providing them the same information and invitation.

8.0 COLLABORATION WITH EUnetHTA WPs

For the individual pilot rapid assessment, no collaboration with other WPs is planned.

9.0 RESOURCE PLANNING

9.1 HUMAN RESOURCES

Table 9. Human resources

Role	Total number of person days	Source	
		Staff of participating organizations	Subcontracting
Author Health	25 person days	25 person days	-
Author Tech	25 person days	25 person days	-
Author EFF + NMA	45-50 person days	45-50 person days	-
Author Safety	35 person days	35 person days	-
Author IQWiG	To be determined	To be determined	-
Co-author Support overall	60 person days	60 person days	-
Dedicated Reviewer	3 person days each	3 person days each	-
Editor/Medical writer	8 person days	-	8 person days

Coordination	To be determined		

The individuals participating in the production of the assessment will be asked to collect actual person days invested through a timesheet template.

10.0 CONFLICT OF INTEREST MANAGEMENT

All individuals participating in this project will sign the standardized “Conflict of Interest” Statement.

Authors and reviewers who declare conflict of interest will be excluded from parts of or the whole work under this specific topic. However they still may be included in other pilots.

For external experts involved, conflict of interest declarations are collected from them regarding the topic. External experts who declare conflict of interest will be excluded from parts of or the whole work under this specific topic. However they still may be included in other pilots.

11.0 EXPECTED OUTCOME(S)

Project outcome(s)
The capacity of national or regional HTA bodies to collaboratively produce structured rapid core HTA and the translation into local reports will have been proven. Redundancies will have been reduced and therefore efficiency gains achieved. Applicability of the HTA Core Model for Rapid REAs will have been tested during the production of the pilot and the Model accordingly improved. The results of this EUnetHTA assessment/review can be used by policy makers across Europe. Next to this, individual HTA agencies could use the results afterwards in health-economic analyses.

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D. APPENDIX

Appendix 1. New treatments and possible comparators

Abbreviations

CHC	chronic hepatitis C
d	day
DBV	dasabuvir
DCL	daclatasvir
EASL	European Association for the Study of the Liver
EPAR	European public assessment report
HIV	human immunodeficiency virus
LDV	ledipasvir
LTX	liver transplantation
OBV	ombitasvir
PEG	peginterferon alfa
PRV	paritaprevir
RBV	ribavirin
RTV	ritonavir
SIM	simeprevir
SOF	sofosbuvir
SPC	summary of product characteristics
wks	weeks

Table 1: simeprevir (OLYSIO): 1 hard capsule (150 mg)/d

Population	Cirrhosis	HIV Co-infection	Intervention	Duration (wks)
CHC, treatment-naïve and prior relapse, genotype 1 or 4				
	+/-	-	SIM+PEG+RBV	24
	-	+	SIM+PEG+RBV	24
	+	+	SIM+PEG+RBV	48
CHC, prior non-responders (incl. partial and null responders), genotype 1 or 4				
	+/-	+/-	SIM+PEG+RBV	48
CHC, treatment-naïve, prior relapse and prior non-responders (incl. partial and null responders), genotype 1 or 4				
	+/-	+/-	SIM+SOF (±RBV)	12

based on EPAR SPC, last updated 7/4/2015

Table 2: sofosbuvir (SOVALDI): 1 film-coated tablet (400 mg)/d

Population	Cirrhosis	HIV Co-infection	Intervention	Duration (wks)
CHC, genotype 1, 4, 5 or 6				
	n.a.	+/-	SOF+PEG+RBV	12 (up to 24 in special populations)
	n.a.	+/-	SOF+RBV (if ineligible/intolerant to PEG)	24
CHC, genotype 2				
	n.a.	+/-	SOF+RBV	12 (up to 24 in special populations)
CHC, genotype 3				
	n.a.	+/-	SOF+PEG+RBV	12 (up to 24 in special populations)
	n.a.	+/-	SOF+RBV	24
CHC, awaiting liver transplantation (LTX)				
	n.a.	+/-	SOF+RBV	until LTX

based on EPAR SPC, last updated 20/7/2015

Table 3: ledipasvir and sofosbuvir (HARVONI): 1 film-coated tablet (90 mg/400mg)/d

Population	Cirrhosis	HIV Co-infection	Intervention	Duration (wks)
CHC, genotype 1 or 4				
	-	+/-	LDV+SOF	12 (8 or 24 in special populations)
	+ (compensated)	+/-	LDV+SOF	24 (12 in special populations)
	+ (decompensated or pre-/post-LTX)	+/-	LDV+SOF+RBV	24
CHC, genotype 3				
	+ and/or prior treatment failure	+/-	LDV+SOF+RBV	24

based on EPAR SPC, last updated 24/4/2015

Table 4: ombitasvir+paritaprevir+ritonavir (VIEKIRAX): 1x2 film-coated tablets (12,5 mg/75 mg/50 mg)/d

Population	Cirrhosis	HIV Co-infection	Intervention	Duration (wks)
CHC, genotype 1a				
	-	+/-	OBV+PRV+RTV+DBV+RBV	12
	+ (compensated)	+/-	OBV+PRV+RTV+DBV+RBV	24
CHC, genotype 1b				
	-	+/-	OBV+PRV+RTV+DBV	12
	+ (compensated)	+/-	OBV+PRV+RTV+DBV+RBV	12
CHC, genotype 4				
	-	+/-	OBV+PRV+RTV+RBV	12
	+ (compensated)	+/-	OBV+PRV+RTV+RBV	24

based on EPAR SPC, 9/3/2015

Table 5: dasabuvir (EXVIERA): 2x1 film-coated tablet (250mg)/d

Population	Cirrhosis	HIV Co-infection	Intervention	Duration (wks)
CHC, genotype 1a				
	-	+/-	DBV+OBV+PRV+RTV+RBV	12
	+ (compensated)	+/-	DBV+OBV+PRV+RTV+RBV	24
CHC, genotype 1b				
	-	+/-	DBV+OBV+PRV+RTV	12
	+ (compensated)	+/-	DBV+OBV+PRV+RTV+RBV	12

based on EPAR SPC, last updated 12/2/2015

Table 6: daclatasvir (DAKLINZA): 1 film-coated tablet (60 mg)/d

Population	Cirrhosis	HIV Co-infection	Intervention	Duration (wks)
CHC, genotype 1 or 4				
	-	n.a.	DCL+SOF	12 (24 in special populations)
	+ (compensated)	n.a.	DCL+SOF	24 (12 in special populations; +RBV in special populations)
CHC, genotype 3				
	+ (compensated) and/or treatment experienced	n.a.	DCL+SOF+RBV	24
CHC, genotype 4				
	n.a.	n.a.	DCL+PEG+RBV	24

based on EPAR SPC, last updated 15/7/201

INTENDED COMPARISONS (based on EASL Clinical Practice Guidelines 2015)

GENOTYPE 1

- **without cirrhosis**
  - SOF+PEG+RBV (12 wks) vs.
  - SIM+PEG+RBV (12 wks) (treatment-naïve or relapsers) or
    SIM+PEG+RBV (24 wks) (partial or null responders) vs.
  - LDV+SOF (8-12 wks) vs.
  - OBV+PRV+RTV+DBV+RBV (12 wks) (genotype 1a) or
    OBV+PRV+RTV+DBV (12 wks) (genotype 1b) vs.
  - SIM+SOF (12 wks) vs.
  - DCL+SOF (12 wks) vs.
  - PEG+RBV (24 or 48 wks) vs.
  - boceprevir+PEG+RBV (28 or 48 wks) vs.
  - telaprevir+PEG+RBV (24 or 48 wks) vs.
  - best supportive care (watchful waiting)

- **with compensated cirrhosis**
  - SOF+PEG+RBV (12 wks) vs.
  - SIM+PEG+RBV (12 wks) (treatment-naïve or relapsers) or
    SIM+PEG+RBV (24 wks) (partial or null responders) vs.
  - LDV+SOF+RBV (12 wks) or
    LDV+SOF (24 wks) or
    LDV+SOF+RBV (24 wks) (if negative predictors of response) vs.
  - OBV+PRV+RTV+DBV+RBV (24 wks) (genotype 1a) or
    OBV+PRV+RTV+DBV+RBV (12 wks) (genotype 1b) vs.
  - SIM+SOF+RBV (12 wks) or
    SIM+SOF (24 wks) vs.
  - DCL+SOF+RBV (12 wks) or
    DCL+SOF (24 wks) vs.
  - PEG+RBV (24 or 48 wks) vs.
  - boceprevir+PEG+RBV (48 wks) vs.
  - telaprevir+PEG+RBV (48 wks) vs.
  - best supportive care (watchful waiting)

- **prior treatment failure (either boceprevir or telaprevir+PEG+RBV)**
  - LDV+SOF+RBV (12 wks) vs. DCL+SOF+RBV (12 wks)

- **prior treatment failure (SOF or SOF+RBV or SOF+PEG+RBV)**
  - LDV+SOF+RBV (12 wks) vs. OBV+PRV+RTV+DBV+RBV (12 wks) vs. SIM+SOF+RBV (12 wks) vs. DCL+SOF+RBV (12 wks)
  - *if F3 or cirrhosis:* LDV+SOF+RBV (24 wks) vs. OBV+PRV+RTV+DBV+RBV (24 wks) vs. SIM+SOF+RBV (24 wks) vs. DCL+SOF+RBV (24 wks)

- **prior treatment failure (SIM+PEG+RBV or SIM+SOF)**
  - LDV+SOF+RBV (12 wks) vs. DCL+SOF+RBV (12 wks)
  - *if F3 or cirrhosis:* LDV+SOF+RBV (24 wks) vs. DCL+SOF+RBV (24 wks)

- **prior treatment failure (OBV+PRV+RTV+DBV)**
  - LDV+SOF+RBV (12 wks) vs. SIM+SOF+RBV (12 wks) vs. DCL+SOF+RBV (12 wks)
  - *if F3 or cirrhosis:* LDV+SOF+RBV (24 wks) vs. SIM+SOF+RBV (24 wks) vs. DCL+SOF+RBV (24 wks)

GENOTYPE 2

- **without cirrhosis**
  - SOF+PEG+RBV (12 wks) vs.
  - SOF+RBV (12 wks) vs.
  - DCL+SOF (12 wks) vs.
  - PEG+RBV (16 or 24 wks) vs.
  - best supportive care (watchful waiting)

- **with compensated cirrhosis**
  - SOF+PEG+RBV (12 wks) vs.
  - SOF+RBV (16-20 wks) vs.
  - DCL+SOF (12 wks) vs.
  - PEG+RBV (16 or 24 wks) vs.
  - best supportive care (watchful waiting)

GENOTYPE 3

- **without cirrhosis**
  - SOF+PEG+RBV (12 wks) vs.
  - SOF+RBV (24 wks) vs.
  - DCL+SOF (12 wks) vs.
  - PEG+RBV (16 or 24 wks) vs.
  - best supportive care (watchful waiting)

- **with compensated cirrhosis**
  - SOF+PEG+RBV (12 wks) vs.
  - DCL+SOF+RBV (24 wks) vs.
  - PEG+RBV (16 or 24 wks) vs.
  - best supportive care (watchful waiting)

GENOTYPE 4

- **without cirrhosis**
  - SOF+PEG+RBV (12 wks) vs.
  - SIM+PEG+RBV (12 wks) (treatment-naïve or relapsers) or SIM+PEG+RBV (24 wks) (partial or null responders) vs.
  - LDV+SOF (12 wks) vs.
  - OBV+PRV+RTV+RBV (12 wks) vs.
  - SIM+SOF (12 wks) vs.
  - DCL+SOF (12 wks) vs.
  - PEG+RBV (24 or 48 wks) vs.
  - best supportive care (watchful waiting)

- **with compensated cirrhosis**
  - SOF+PEG+RBV (12 wks) vs.
  - SIM+PEG+RBV (12 wks) (treatment-naïve or relapsers) or SIM+PEG+RBV (24 wks) (partial or null responders) vs.
  - LDV+SOF+RBV (12 wks) or LDV+SOF (24 wks) or LDV+SOF+RBV (24 wks) (if negative predictors of response) vs.
  - OBV+PRV+RTV+RBV (24wks) vs.
  - SIM+SOF+RBV (12 wks) or SIM+SOF (24 wks) vs.
  - DCL+SOF+RBV (12 wks) or DCL+SOF (24 wks) vs.
  - PEG+RBV (24 or 48 wks) vs.
  - best supportive care (watchful waiting)

- **prior treatment failure (SOF or SOF+RBV or SOF+PEG+RBV)**
  - LDV+SOF+RBV (12 wks) vs. OBV+PRV+RTV+RBV (12 wks) vs. SIM+SOF+RBV (12 wks) vs. DCL+SOF+RBV (12 wks)
  - *if F3 or cirrhosis:* LDV+SOF+RBV (24 wks) vs. OBV+PRV+RTV+RBV (24 wks) vs. SIM+SOF+RBV (24 wks) vs. DCL+SOF+RBV (24 wks)

- **prior treatment failure (SIM+PEG+RBV or SIM+SOF)**
  - LDV+SOF+RBV (12 wks) vs. DCL+SOF+RBV (12 wks)
  - *if F3 or cirrhosis:* LDV+SOF+RBV (24 wks) vs. DCL+SOF+RBV (24 wks)

- **prior treatment failure (OBV+PRV+RTV)**
  - LDV+SOF+RBV (12 wks) vs. SIM+SOF+RBV (12 wks) vs. DCL+SOF+RBV (12 wks)
  - *if F3 or cirrhosis:* LDV+SOF+RBV (24 wks) vs. SIM+SOF+RBV (24 wks) vs. DCL+SOF+RBV (24 wks)

GENOTYPE 5 OR 6

- **without cirrhosis**
  - SOF+PEG+RBV (12 wks) vs.
  - LDV+SOF (12 wks) vs.
  - DCL+SOF (12 wks) vs.
  - PEG+RBV (48 wks) vs.
  - best supportive care (watchful waiting)

- **with compensated cirrhosis**
  - SOF+PEG+RBV (12 wks) vs.
  - LDV+SOF+RBV (12 wks) or
    LDV+SOF (24 wks) or
    LDV+SOF+RBV (24 wks) (if negative predictors of response) vs.
  - DCL+SOF+RBV (12 wks) or
    DCL+SOF (24 wks) vs.
  - PEG+RBV (48 wks) vs.
  - best supportive care (watchful waiting)

- **prior treatment failure (SOF or SOF+RBV or SOF+PEG+RBV or DCL+PEG+RBV or DCL+SOF or LDV+SOF)**
  - LDV+SOF+RBV (12 wks) vs. DCL+SOF+RBV (12 wks)
  - *if F3 or cirrhosis:* LDV+SOF+RBV (24 wks) vs. DCL+SOF+RBV (24 wks)

SPECIAL POPULATIONS (based on EASL Clinical Practice Guidelines 2015)

WITH DECOMPENSATED CIRRHOSIS, WITHOUT INDICATION FOR LTX

- **genotype 2**
  - SOF+RBV (16-20 wks) vs. DCL+SOF+RBV (12 wks)

- **genotype 1, 4, 5 or 6**
  - LDV+SOF (12 wks) vs. DCL+SOF+RBV (12 wks)
  - *if contraindications to RBV:* LDV+SOF (12 wks) vs. DCL+SOF (24 wks)

WITH HCC WITH COMPENSATED CIRRHOSIS, AWAITING LTX

- **genotype 1**
  - LDV+SOF+RBV (12 wks) vs.
  - OBV+PRV+RTV+DBV+RBV (12 wks) (genotype 1b) or
    OBV+PRV+RTV+DBV+RBV (24 wks) (genotype 1a) vs.
  - SIM+SOF+RBV (12 wks) vs.
  - DCL+SOF+RBV (12 wks) vs.
  - SOF+PEG+RBV (12 wks)

- **genotype 2**
  - SOF+RBV (16-20 wks) vs.
  - DCL+SOF+RBV (12 wks) vs.
  - SOF+PEG+RBV (12 wks)

- **genotype 4**
  - LDV+SOF+RBV (12 wks) vs.
  - OBV+PRV+RTV+RBV (12 wks) vs.
  - SIM+SOF+RBV (12 wks) vs.
  - DCL+SOF+RBV (12 wks) vs.
  - SOF+PEG+RBV (12 wks)

- **genotype 5 or 6**

- LDV+SOF+RBV (12 wks) vs.
- DCL+SOF+RBV (12 wks) vs.
- SOF+PEG+RBV (12 wks)

WITH DECOMPENSATED CIRRHOSIS, AWAITING LTX

- **genotype 1, 4, 5 or 6**
  - LDV+SOF+RBV (12 wks) vs. DCL+SOF+RBV (12 wks)

- **genotype 2**
  - SOF+RBV (12 wks) vs. DCL+SOF+RBV (12 wks)

POST-LTX, WITHOUT CIRRHOSIS OR WITH COMPENSATED CIRRHOSIS, WITHOUT NEED FOR IMMUNOSUPPRESSANT DRUG DOSE ADJUSTMENT

- **genotype 1, 4, 5 or 6**
  - LDV+SOF+RBV (12 wks) vs. DCL+SOF+RBV (12 wks)

- **genotype 2**
  - SOF+RBV (12 wks) vs. DCL+SOF+RBV (12 wks)

POST-LTX, WITHOUT CIRRHOSIS OR WITH COMPENSATED CIRRHOSIS, WITH NEED FOR IMMUNOSUPPRESSANT DRUG DOSE ADJUSTMENT OR AVOIDANCE OF CYCLOSPORINE A (SIM+SOF)

- **genotype 1**
  - OBV+PRV+RTV+DBV+RBV (12 wks) (genotype 1b) or
    OBV+PRV+RTV+DBV+RBV (24 wks) (genotype 1a with cirrhosis) vs.
  - SIM+SOF+RBV (12 wks)

- **genotype 4**
  - OBV+PRV+RTV+RBV (12 or 24 wks) vs. SIM+SOF+RBV (12 wks)

POST-LTX, WITH DECOMPENSATED CIRRHOSIS

- **genotype 1, 4, 5 or 6**
  - LDV+SOF+RBV (12 wks) vs. DCL+SOF+RBV (12 wks)

- **genotype 2**
  - SOF+RBV (12 wks) vs. DCL+SOF+RBV (12 wks)

HBV CO-INFECTION

Please refer to comparisons for HCV monoinfected patients.

Appendix 2. Template for data extraction

The template below was developed together with EMA in order to uniformly present data from studies and make is easier for HTA agencies to use the work that is already done by EMA.

<table>
<tr><td colspan="3"><u>Title:</u> <title> {as indicated on the study report}</td></tr>
<tr><td>Study identifier</td><td colspan="2"><code>
{list all codes starting with the protocol number followed by – as available - EudraCT number, ISRCT number, other codes that allow cross-referencing to publications}</td></tr>
<tr><td>Study population</td><td colspan="2">Include variables of relevance for chronic hepatitis C, eg genotype/subtype of HCV, treatment-naïve or experienced, cirrhosis or no cirrhosis, and as appropriate, HIV co-infected, post-transplant,..</td></tr>
<tr><td rowspan="2">Design</td><td colspan="2"><free text>
{describe key elements of the design (cross-over, parallel, factorial, dose-escalation, fixed-dose response) including randomisation, blinding, allocation concealment, mono-/multi-centre, etc.}</td></tr>
<tr><td>Duration of main phase:</td><td><time></td></tr>
</table>

Title: <title> *{as indicated on the study report}*			
Study identifier	<code> *{list all codes starting with the protocol number followed by – as available - EudraCT number, ISRCT number, other codes that allow cross-referencing to publications}*		
	Duration of Run-in phase: Duration of Extension phase:	<time> <not applicable> <time> <not applicable>	
Hypothesis	<Superiority> < Equivalence> <Non-inferiority> <Exploratory: specify>		
Treatments groups *{add as many rows as needed to describe the treatment groups}*	<group descriptor> *{provide abbreviation for use later in the table of the results section}*		<treatment>. <duration>, <number randomised>
	<group descriptor>		<treatment>. <duration>, <number randomized>
	<group descriptor>		<treatment>. <duration>, <number randomised>
Endpoints and definitions *{add as many rows as needed to describe the endpoints; for the secondary endpoints select the ones considered most relevant and reported in the results section}*	<Co->Primary endpoint	<label> *{generate abbreviation for use later in the table of the results section}*	<free text> *{provide brief description}*
	<Secondary> <other: specify> endpoint	<label>	<free text> *{provide brief description}*
	<Secondary> <other: specify> endpoint	<label>	<free text> *{provide brief description}*
Database lock	<date>		

Results and Analysis
{present the result separate for each analysis that is considered relevant for the conclusion on the trial; in any case the pre-specified primary analysis should be presented}

Analysis description	**Primary Analysis**			
Analysis population and time point description	<Intent to treat> <Per protocol> <other: specify> *{consider adding a brief description of the definition of the population}* <time point>			
Descriptive statistics and estimate variability	Treatment group	<group descriptor> *{as per above terminology}*	<group descriptor> *{as per above terminology}*	<group descriptor> *{as per above terminology}*
	Number of subject	<n>	<n>	<n>
	<endpoint> *{label as above}* (<statistic>) *{e.g. mean, median, etc}*	<point estimate>	<point estimate>	<point estimate>
	<variability statistic> *{e.g. standard deviation, confidence interval, etc}*	<variability>	<variability>	<variability>

<table>
<tr><td colspan="6"><u>Title:</u> <u><title></u> {as indicated on the study report}</td></tr>
<tr><td>Study identifier</td><td colspan="5"><code>
{list all codes starting with the protocol number followed by – as available - EudraCT number, ISRCT number, other codes that allow cross-referencing to publications}</td></tr>
<tr><td></td><td><endpoint> (<statistic>)</td><td><point estimate></td><td><point estimate></td><td><point estimate></td></tr>
<tr><td></td><td><variability statistic></td><td><variability></td><td><variability></td><td><variability></td></tr>
<tr><td></td><td><endpoint> (<statistic>)
<variability statistic></td><td><point estimate>
<variability></td><td><point estimate>
<variability></td><td><point estimate>
<variability></td></tr>
<tr><td rowspan="11">Effect estimate per comparison
{add as many rows as needed to describe the relevant statistical testing performed}</td><td rowspan="4"><Co->Primary endpoint</td><td>Comparison groups</td><td colspan="3"><group descriptors>
{as per above terminology}</td></tr>
<tr><td><test statistic> {e.g. difference between groups}</td><td colspan="3"><point estimate></td></tr>
<tr><td><variability statistic> {e.g. confidence interval, etc}</td><td colspan="3"><variability></td></tr>
<tr><td>P-value{indicate statistical test used, e.g. ANOVA}</td><td colspan="3"><P-value></td></tr>
<tr><td rowspan="4"><<Co->Primary > <Secondary><other: specify> endpoint
{indicate endpoint using terminology as per section “Endpoint and definitions}</td><td>Comparison groups</td><td colspan="3"><group descriptors></td></tr>
<tr><td><test statistic></td><td colspan="3"><point estimate></td></tr>
<tr><td><variability statistic></td><td colspan="3"><variability></td></tr>
<tr><td>P-value</td><td colspan="3"><P-value></td></tr>
<tr><td rowspan="4"><<Co->Primary > <Secondary><other: specify> endpoint</td><td>Comparison groups</td><td colspan="3"><group descriptors></td></tr>
<tr><td><test statistic></td><td colspan="3"><point estimate></td></tr>
<tr><td><variability statistic></td><td colspan="3"><variability></td></tr>
<tr><td>P-value</td><td colspan="3"><P-value></td></tr>
<tr><td>Notes</td><td colspan="5"><free text>
{consider amongst others the following information:
- reasons for drop-outs
- critical findings with regard to the analysis}</td></tr>
<tr><td>Analysis description</td><td colspan="5"><Secondary analysis> <Co-primary Analysis> <Other, specify: > {also indicate if the conduct of the analysis was pre-specified}</td></tr>
<tr><td>{repeat all the above sections for each analysis that is considered relevant}</td><td colspan="5"></td></tr>
</table>

For data extraction of adverse events, the tables in the publications will be copied.

Abbreviations:
Sources: