



# eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA 21

**Project Plan**

**D4.5 APPLICABILITY OF EVIDENCE**

**Version 1.0, 03/12/2021**  
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## DOCUMENT HISTORY AND CONTRIBUTORS

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### Disclaimer

This Project Plan was produced under the Third EU Health Programme through a service contract with the European Health and Digital Executive Agency (HaDEA) acting under the mandate from the European Commission. The information and views set out in this Project Plan are those of the author(s) and do not necessarily reflect the official opinion of the Commission/ Executive Agency. The Commission/Executive Agency do not guarantee the accuracy of the data included in this study. Neither the Commission /Executive Agency nor any person acting on the Commission's / Executive Agency's behalf may be held responsible for the use which may be made of the information contained therein.

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The work in EUnetHTA 21 is a collaborative effort. While the agencies in the Hands-on Group will be actively writing the deliverable, the entire EUnetHTA 21 consortium is involved in its production throughout various stages. This means that the Committee for Scientific Consistency and Quality (CSCQ) will review and discuss several drafts of the deliverable prior to validation. Afterwards the Consortium Executive Board (CEB) will endorse the final deliverable prior to publication. For further information on stakeholder involvement in this deliverable, please see section 3.2.

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## LIST OF ABBREVIATIONS

CEB	Consortium Executive Board
CSCQ	Committee for Scientific Consistency and Quality
EUnetHTA	European Network of Health Technology Assessment
GRADE	Grading of Recommendation, Assessments, Development and Evaluation
HCP	Healthcare Professionals
HOG	Hands-on Group
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
HTAb	Health Technology Assessment Body
HTD	Health Technology Developer
JA3	Joint Action 3
JCA	Joint Clinical Assessment
JSC	Joint Scientific Consultation
OT	Other Technologies
PICO	Population, Intervention, Comparison and Outcome(s)
pMAH	Prospective Marketing Authorisation Holder
PT	Pharmaceutical Technologies
REA	Relative Effectiveness Assessment
SOP	Standard Operating Procedure

## 1 INTRODUCTION

In the technical offer, submitted on 04/05/2021, deliverables for the production of methodological guidelines have been defined.

This Project Plan describes the objectives, approach and timelines for the deliverable D.4.5 on Applicability of evidence in the context of JCA which includes deliverables D.4.5.1 and D.4.5.2.

## 2 BACKGROUND

JCA/CA are part of an iterative process in which they are neither the starting product nor the end product. Indeed, the ultimate goal of this process is to inform decision-making on reimbursement and/or pricing at a national level. Quality of evidence and the uncertainty thereof are crucial elements informing decision-making.

In 2020 the EUnetHTA Executive Board decided, based on recommendations from the ‘Task Group on Common Phrases and GRADE’, that future JCAs/CAs should not contain overall conclusions – neither on quality or certainty of evidence, nor on the presence of benefit or harm. This decision was made because general conclusions may (unintentionally) imply or predetermine national appraisal and reimbursement decisions. In addition, EUnetHTA provided recommendations for formulations of results of assessments (“common phrases”) that comply with the objectives of being as informative as possible to reduce the workload of member states that use them and, at the same time, allowing for independent contextualisation and decision-making at the national level.

The applicability of clinical evidence may differ because of the final objective and usage of the assessment (i.e. for appraisal of clinical added value or for incremental cost-effectiveness evaluation) between EU member states.

Based on the experience of EUnetHTA partners in JA3 and on the discussions which took place in several of its task groups (e.g. PICO task group or ‘Task Group on Common Phrases and GRADE’), it became clear that it was necessary to complement the work to reach agreement on several topics (see section 3 below).

**Table 2.1. Existing EUnetHTA documents**

Title	Scope
<b>Documents that should be used to produce the deliverable D.4.5</b>	
PICO concept paper, 2020	Conceptualizes EUnetHTA’s perspective on the role of the PICO question(s) for joint evaluations and defines a standard process on how to develop the PICO question(s).
Task Group for Common Phrases and GRADE: GRADE framework paper, 2020	Presents a proposal of standardised presentation of evidence based on partial use of GRADE methodology and partial use thereof, based on the work of and discussions in the Task Group for Common Phrases and GRADE.
Task Group for Common Phrases and GRADE: Common Phrases, 2021	Provides recommendations for formulation of results and conclusions in joint evaluation reports
EUnetHTA SOP “How to Create and Maintain a Methodological Guideline”	Describes the whole process of developing a methodological guideline from topic selection till the publication of the guideline in the Companion Guide and on the EUnetHTA website. Additionally, the SOP describes the maintenance process of guidelines from initiating the revision till the publication of the updated guideline.
EUnetHTA SOP “How to maintain a SOP”	Describes the process to maintain a SOP: from receiving a proposition for a change of an SOP to the publication of the amended SOP in the Companion Guide and the information to the EUnetHTA partners about the revision of the SOP.
<b>SOPs/guidelines potentially impacted (should be checked for consistency with the practical guideline to be developed*)</b>	

EUnetHTA SOP “Scoping and developing project plan” (PT-02-ScopDevPP)	Describes the process steps and responsibilities related to developing the scope of the project and writing the 1st draft of the Project Plan during EUnetHTA Pharmaceutical Technologies (PT) Joint Assessments (JA).
EUnetHTA SOP “Scoping, developing 1 <sup>st</sup> draft of the project plan and submission dossier” (OT-02-ScopDevDPPSubDos)	Describes the process steps and responsibilities related to developing the scope, direction of the project and writing the 1st draft of the project plan (PP).
EUnetHTA SOP “Submission dossier” (PT-02-SubDos)	Describes the process steps to be taken to request a Submission Dossier from the pMAH and how to perform formal check of completeness of the Dossier. Describes the procedures to be initiated if the wording of the licensed indication changes compared to the expected wording during the regulatory process and the Submission Dossier has to be amended.
EUnetHTA SOP “Internal Review of 1st Draft Project Plan” (PT-02-IntRevPP and OT-02-IntRevPP)	Describes the process steps and responsibilities within the internal review (= review by dedicated reviewers) of the 1 <sup>st</sup> draft project plan.
EUnetHTA SOP “Internal review of draft submission dossier” (PT-02-IntRevSD)	Describes how the study pool provided by the pMAH in the submission dossier should be assessed for completeness and for relevance to the research question(s) formulated in the project plan for the assessment.
EUnetHTA SOP: Data Extraction (OT-03-DatExt)	Describes the process steps, responsibilities and timelines related to data extraction in a Rapid Relative Effectiveness Assessment (REA) report. The SOP is valid for collaborative and joint assessments on “Other Technologies” (OT).
EUnetHTA SOP: Data Extraction (PT-03-DatExt)	Describes the process steps, responsibilities and timelines related to data extraction in a (rapid) Relative Effectiveness Assessment (REA) report. The SOP is valid for joint assessments on pharmaceutical technologies.
EUnetHTA SOP “Internal Review of 1st Draft Assessment by Dedicated Reviewers (PT-03-IntRevDA and OT-03-IntRevDA)”	Describes the process steps and responsibilities within the internal review (= review by dedicated reviewers) of the 1st draft assessment.
EUnetHTA guideline: Endpoints used for Relative Effectiveness Assessment: Clinical Endpoints (updated 2015)	To describe the common characteristics of clinical endpoints, issues relating to their measurement and presentation, and to briefly outline some of the problems arising when comparing or pooling clinical endpoint data. To provide recommendations for the selection and the interpretation of clinical endpoints in the context of Relative Effectiveness Assessment (REA).
EUnetHTA guideline: Endpoints used for Relative Effectiveness Assessment Composite endpoints (updated 2015)	To describe the advantages and disadvantages of the use of composite endpoints as opposed to single endpoints and offer guidance for assessors about construction, reporting and interpretation of the results of composite endpoints in the context of REA
EUnetHTA guideline: Endpoints used in Relative Effectiveness Assessment: Surrogate Endpoints (updated 2015)	To provide guidance on when and how surrogate endpoints can be used for REA.
EUnetHTA guideline: Endpoints used in Relative Effectiveness Assessment: Safety (updated 2015)	This guideline focuses on the relative safety assessment performed by the HTA assessors when conducting Relative Effectiveness Assessment (REA) and deals with the following methodological issues: <ul style="list-style-type: none"> <li>• objectives of HTA assessors</li> <li>• terminology</li> <li>• identification of adverse reactions: sources of information</li> <li>• evaluation of sources of information</li> <li>• synthesis and reporting of results compared to other interventions</li> </ul>

<p>EUnetHTA guideline: Endpoints used for Relative Effectiveness Assessment: Health related quality of life and utility measures (updated 2015)</p>	<p>(1) Support assessors in identifying the strengths and weaknesses in the evidence provided and (2) inform researchers about the requirements regarding HRQoL assessment to allow them to anticipate the collection of the required data for REA when developing trial protocols.</p>
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\*this list is seen as a minimum to be checked, other SOPs/guidelines might be identified by the hands-on group and subject to update

### 3 OBJECTIVE AND METHODS

For all of the objectives below the future EU HTA regulation will serve as the basis and the past JA3 experiences will be taken into account.

The objectives of this deliverable are to:

- Consensually develop a practical guideline (sub-deliverable 4.5.1) for critical assessment of evidence regarding the following issues that are regularly raised during JCAs/CAs:
  - How to consider complementary analysis (e.g. subgroup analysis, post hoc analysis, sensitivity analysis);
  - How to handle multiplicity issues resulting from multiple testing, e.g. due to multiple subgroup analyses, comparisons across multiple treatment arms and analyses of multiple outcomes?

These issues were identified based on:

- the work done by the GRADE task group and the PICO task group and the corresponding documents recently produced by EUnetHTA during JA3 (i.e. “GRADE framework paper”, “Common phrases” and “PICO concept paper”);
- feed-back of the members of the Consortium for Project 21 on their experience in JA3 with JCA/CA and Early Dialogues, gathered when preparing the offer to the European Commission.

Other aspects relevant for the critical assessment of evidence might also be discussed, if deemed relevant by the HOG.

- Check the existing EUnetHTA guidelines/SOPs (see Table 2.1) for consistency with the practical guideline and consider updates (sub-deliverable 4.5.2).

#### 3.1 *Methods to achieve the objectives*

Deliverable D4.5 is composed of two sub-deliverables:

- Sub-deliverable D4.5.1: A practical guideline on how to handle complementary analysis and multiplicity issues will be produced. The work done by the GRADE task group and the PICO task group will be used as a basis for discussion and complemented by practical guidance on how to address the issues mentioned above (other aspects relevant for the critical assessment of evidence might also be discussed, if deemed relevant by the HOG). Relevant literature will be identified through an unsystematic literature search. Then, the practical guideline will be consensually developed in the HOG through iterative discussions and a proposition will be submitted to the CSCQ for review;
- Sub-deliverable D4.5.2: The existing EUnetHTA guidelines/SOPs (see Table 2.1) will be checked for consistency with the practical guideline and updates will be considered, based on the SOPs listed in the procedure for CSCQ.

#### 3.2 *Stakeholder inclusion*

EUnetHTA 21 Stakeholder Pool is composed of HTA bodies (HTAb) outside of EUnetHTA 21 consortium, as well as stakeholder groups on patients, health technology developers (HTD), healthcare professionals (HCP), payers, and regulatory agencies from the EU/EEA countries.

Non-consortium HTAb (i.e. those not part of the EUnetHTA 21 consortium) who will be involved in the future subgroups of the HTA Regulation, should participate in the development of this project in order to ensure the deliverables are applicable to all European HTAb. They should be consulted at the beginning of the project. Additionally, they will be invited to review, at the same time as the Committee for Scientific Consistency and Quality (CSCQ), the 1st draft of the deliverable and the pre-final draft that will be submitted for public consultation.

Other members of the EUnetHTA 21 Stakeholder pool will also be involved in this project. Their involvement will include, at minimum, participation in an informational kick-off meeting and regular stakeholder fora. They will also be invited to contribute to the work through public consultation.

## 4 ORGANISATION OF THE WORK

### 4.1 Mode of collaboration and frequency of meetings

The work will be distributed evenly between the agencies of the hands-on group (HOG). All HOG members will review each other's work prior to review by the CSCQ. The HOG will appoint one agency to interact with the three CSCQ configurations and the CEB.

The HOG will have meetings/email updates when needed, but at least monthly meetings, to update each other on the progress. In addition, when needed, the HOG will also have regular meetings with the other relevant HOGs.

### 4.2 Timelines

Table 4.1. Timetable

Milestones	Start date	End date
Project duration	21/01/2022	04/11/2022
1st Draft deliverable	21/01/2022	23/03/2022
Public consultation	04/07/2022	02/08/2022
Validate final version deliverable (CSCQ)		18/10/2022
Endorsement final version deliverable (CEB)		02/11/2022
Estimated finalisation date of the deliverable date *		04/11/2021

\*publication date may fluctuate depending on the outcome of the Consortium Executive Board endorsement