eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA 21

**Project Plan**

# D4.6 VALIDITY OF CLINICAL STUDIES

**Version 1.0, 03/12/2021**
Template version 1.0, 30/09/2021

# DOCUMENT HISTORY AND CONTRIBUTORS

| Version | Date | Description |
|---|---|---|
| **V1.0** | **03/12/2021** | Final Project Plan |

### Disclaimer



### Participants

| | |
|---|---|
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| **CEB** | |

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.

### Copyright

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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 |
| NRS | Non-randomised Studies |
| PICO | Population, Intervention, Comparison and Outcome(s) |
| pMAH | Prospective Marketing Authorisation Holder |
| PP | Project Plan |
| PT | Pharmaceutical Technologies |
| RCT | Randomised Controlled Trial |
| REA | Relative Effectiveness Assessment |
| RoB | Risk of Bias |
| 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.4.6 on Validity of clinical studies which includes deliverables D.4.6.1 and D.4.6.2.

# 2 BACKGROUND

Randomised Controlled Trials (RCT) are the gold standard to determine the relative effects of interventions due to their high internal validity. However, in some situations RCTs have not (yet) been or cannot be conducted. In these cases, it is important to know under what conditions sufficiently valid effects can be derived from non-randomised evidence. Therefore, it is crucial to know the strengths and weaknesses of these types of non-randomised studies.

Consideration of various study designs in the body of evidence for assessment implies discussion around non-randomised trials, single-arm trials, and innovative/non-classical study designs, such as basket trials (e.g. for treatments of histology-independent indications, so called “agnostic” indications).

It is also important to agree on how to consider real-world evidence in the assessment reports. During the initial assessment of a medicinal product or a high-risk medical device, the available data come primarily from clinical trials, and data obtained in real-life use conditions are rare (essentially data from early access program/compassionate use depending on the country). However, results of post-registration studies might be available in case of re-assessment.

In 2020, the EUnetHTA Executive Board concluded that GRADE (or any other system for rating the overall quality of the evidence and developing health care recommendations) can only partly be applied within EUnetHTA because overall conclusions or recommendations might interfere with the independent contextualisation and decision-making at the national level. However, valid scientific principles are still required, not only to guide the development of the JCA/CA at the European level, but also to support the understandability and usability of these results for national decision-making. Therefore, additional guidance is needed.

**Table 2.1. Existing EUnetHTA documents**

| Title | Scope |
|---|---|
| **Documents that should be used to produce the deliverable D.4.6** | |
| 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 guideline: Internal validity of randomised controlled trials (updated 2015) | To provide recommendations for the assessment of the internal validity of RCTs whose purpose is the determination of the relative effectiveness of health care interventions |
| EUnetHTA guideline: Internal validity of non-randomised studies (NRS) on interventions (updated 2015) | To provide recommendations on the assessment of the internal validity of NRS used for the evaluation of effects of interventions |
| SOP: Risk of Bias Assessment of Clinical Studies (updated 2019) | To describe the process steps, responsibilities and timelines related to the Risk of Bias (RoB) assessment |

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| | of clinical studies in the generation of the domains effectiveness/efficacy and safety in a rapid Relative Effectiveness Assessment (REA). |
| Concept paper on a planned guideline 'Critical assessment of clinical evidence', 2019 | A concept paper on a planned methodological guideline "critical assessment of clinical evidence" was developed in 2019 by EUnetHTA. However, the guideline could not be produced due to organisational reasons. One of the main subjects identified to be discussed in this paper was what are the strengths and weaknesses of different study designs and how to handle them. |
| 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. |
| **SOPs/guidelines potentially impacted (should be checked for consistency with the practical guideline to be developed*)** | |
| 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 1st draft of the project plan and submission dossier" (OT-02-ScoDevDPPSubDos) | 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 1st 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:<br>Clinical Endpoints<br>(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. |

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| | 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<br>Composite endpoints<br>(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<br>(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<br>(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:<br>• objectives of HTA assessors<br>• terminology<br>• identification of adverse reactions: sources of information<br>• evaluation of sources of information<br>• synthesis and reporting of results compared to other interventions |
| EUnetHTA guideline: Endpoints used for Relative Effectiveness Assessment: Health related quality of life and utility measures (updated 2015) | (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. |

*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 on how to consider, classify and label various types of evidence in the assessment reports, including real world data and data from basket trials, to support authors of JCA/CA in understanding, selecting, and critically appraising clinical evidence. This will also address the general principles which determine the certainty of results (e.g. internal validity, external validity, and statistical precision). These topics were identified based on the Concept paper on a planned guideline 'Critical assessment of clinical evidence', 2019 and the 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;

- Check the existing EUnetHTA guidelines/SOPs (see Table 2.1) for consistency with the practical guideline and consider updates (sub-deliverable 4.6.2).

## *3.1 Methods to achieve the objectives*

Deliverable D4.6 comprised two sub-deliverables:

- Sub-deliverable D4.6.1: A practical guideline on how to consider, classify and label various types of evidence in the assessment reports, including real world data and data from basket trials, will be produced. This will also address the general principles which determine the certainty of results (e.g. internal validity, external validity, and statistical precision). The guideline concept paper 'Critical assessment of clinical evidence' developed in JA3 will be used as a basis for discussion

and other relevant aspects related to the validity of clinical studies will be considered. Relevant literature will be identified through an unsystematic literature search and a review of the recent dossiers that contains non-classical evidence (either dossiers seen in JCAs during JA3 or seen at national level by members of the HOG) will be performed. 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 D4.6.2: 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 *** | 04/11/2022 | |

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