EUnetHTA 21

Project Plan

D4.4 ENDPOINTS

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DOCUMENT HISTORY AND CONTRIBUTORS

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

Disclaimer

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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
HCP	Healthcare Professionals
HOG	Hands-on Group
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, Comparator, Outcome
pMAH	Prospective Marketing Authorisation Holder
PT	Pharmaceutical Technologies
QoL	Quality of Life
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.4.4 on Endpoints which includes deliverables D.4.4.1 and D.4.4.2.

2 BACKGROUND

Discussions around the endpoints in JCA/CA starts from the drafting of the PICO questions and are pursued during the assessment phase.

Five methodological guidelines exist that specifically deal with endpoints (see Table 2-1 for the description of the content of each one). The existing guidelines describe the characteristics of different types of endpoints (clinical endpoints including health related quality of life, safety endpoints…) and issues relating to their measurement and presentation. Specificities related to surrogate endpoints are also discussed. These also provide recommendations for the selection and interpretation of clinical endpoints when conducting a REA.

Based on experience of partners in JA3 when performing JCA/CA and JSC, divergent views were identified on the following topics, that need to be addressed in a practical guideline for the authors: how to determine meaningful clinical endpoints when drafting the PICO, is there some therapeutic areas or clinical contexts for which specificities can be highlighted in terms of clinical relevance of the endpoints, what would be the requirement for safety outcomes, and how to consider and assess surrogate/intermediate endpoints. Discussion topics that frequently aroused during assessment (and also during early dialogues (now Joint Scientific Consultations) include for example:

- the use of an intermediate outcome measure without demonstration of a link with a relevant clinical endpoint (for example, in the field of oncology, progression-free survival in situations whereby overall survival cannot be documented in the short or medium-term);
- the use of a surrogate endpoint (in particular a biomarker) and the demonstration of link with the respective clinical morbidity and mortality endpoints.
- what is expected to assess the validity of a scale as a measure of a clinical endpoint;
- what is the information needed for interpretation of the results in term of clinical relevance;
- place of external recommendations and guidelines (for example from regulatory bodies or research project or patients' associations) for the choice of endpoints, in order to ensure clinical relevance, further usage of endpoint in real practice, less missing data and indirect comparison between treatments.

Table 2.1. Existing EUnetHTA documents

Title	Scope
Documents that should be used to produce the deliverable D.4.4	
Partial use of GRADE in EUnetHTA – Framework paper (2020)	Describes the requirements for partial use of GRADE in JCA/CA
Recommendations for Early Dialogues based on the Experience of EUnetHTA Joint Action 3 (2021)	This report aims to provide an overview of the work that has been carried out within WP5A in Joint Action 3 and to provide recommendations based on the experience and lessons learned.
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*)	
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).
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
Endpoints used in Relative Effectiveness Assessment: Surrogate Endpoints (updated 2015)	To provide guidance on when and how surrogate endpoints can be used for REA.
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: • objectives of HTA assessors • terminology • identification of adverse reactions: sources of information • evaluation of sources of information • synthesis and reporting of results compared to other interventions
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.
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.

* 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 develop a practical guideline (sub-deliverable 4.4.1) on how to deal with the several issues encountered around the assessment of endpoints in JCAs/CAs. In particular the following subjects should be settled down: establishment of a common definition of meaningful clinical endpoints when drafting the PICO; definition of requirements for safety endpoints; identification of determinant endpoints for some therapeutic areas or clinical contexts, if applicable; how to consider and assess surrogate/intermediate endpoints. It could be considered also to develop some items related to Patient-reported Outcome Measures, validity of scales and information needed for interpretation of the results in term of clinical relevance, and place of external recommendations and guidelines for the choice of endpoints (see 3.1);

- To check the existing EUnetHTA guidelines/SOPs (see Table 2.1.) for consistency with the practical guideline and consider updates (sub-deliverable 4.4.2).

3.1 Methods to achieve the objectives

Deliverable D4.4 comprised two sub-deliverables:

Sub-deliverable D4.4.1: A practical guideline on issues encountered around the assessment of endpoints in JCAs/CAs will be produced. These issues were identified based on:

- documents recently produced by EUnetHTA during JA3 (i.e. "GRADE framework paper": discussions on interpretation of the results, "Final recommendations for Early Dialogues": discussions around the need for method adaptation for PROs including QoL, information needed for interpretation of the results in term of clinical relevance);
- 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 (e.g. requirement for safety outcomes).

At the start of the work, a survey among CSCQ members will be perform, to collect their feed-back on national practice on the subjects defined in the Project Plan. Relevant literature and external initiatives 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 D4.4.2: 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	22/04/2022	13/01/2023
1st Draft deliverable	22/04/2022	22/06/2022
Public consultation	03/10/2022	01/11/2022
Validate final version deliverable (CSCQ)	13/12/2022	
Endorsement final version deliverable (CEB)	11/01/2023	
Estimated finalisation date of the deliverable *	13/01/2023	

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