EUnetHTA 21

**Project Plan**

# D4.3 COMPARATORS AND COMPARISONS

**Version 1.0, 03/12/2021**
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# 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 |
| HCP | Healthcare Professionals |
| HOG | Hands-on Group |
| HTA | Health Technology Assessment |
| HTAb | Health Technology Assessment Body |
| HTD | Health Technology Developer |
| ITC | Indirect Treatment Comparisons |
| JCA | Joint Clinical Assessment |
| JSC | Joint Scientific Consultation |
| MAIC | Matching Adjusted Indirect Comparison |
| REA | Relative Effectiveness Assessment |
| SOP | Standard Operating Procedure |
| STC | Simulated Treatment Comparison |

# 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 deliverables corresponding to section 4.3 on Comparators and Comparisons.

# 2 BACKGROUND

The EUnetHTA methodological guideline 'Comparators & Comparisons: Direct and indirect comparisons', updated in 2015, focusses on the methods available for treatment comparisons. Their strengths and limitations are discussed and recommendations are provided in order to support rapid REAs in their activity. The guideline describes networks of evidence, methods of direct and indirect comparison, and finally provides an overview of considerations that should be taken into account when carrying out a comparison. Direct methods relate to evidence synthesis of multiple trials or studies with head-to-head evidence between the intervention and comparator of interest. Indirect methods are needed when there is an absence of head-to-head data between the intervention and comparator of interest (e.g., when it is wished to compare active treatments but all the available data are based on two-arm placebo-controlled trials). Network meta-analyses facilitate the combination of direct and indirect evidence to estimate treatment effects for all pairs of included interventions. There are a wide variety of methodologies available underpinned by assumptions that do not always hold in practice. Given that evidence synthesis of treatment effect is a major component of a REA, the appropriate application of direct and indirect comparison methods is critical.

Since the first publication of the EUnetHTA guideline 'Comparators & Comparisons: Direct and indirect comparisons' in 2013, it has been subject to minimal updating in terms of content and format in 2015. Based on feedback received from assessment teams, methodological experts based in HTA agencies and external stakeholders, it has been identified by EUnetHTA partners during JA3 that the guideline needed to be updated to include other existing methodologies for direct treatment comparisons, such as the Knapp-Hartung method, and indirect treatment comparisons (ITC), such as matching adjusted indirect comparison (MAIC) and simulated treatment comparison (STC). These methodologies are increasingly used in health technology developers' submission to HTA bodies. Especially in the case of disconnected networks, the available ITC methods require very strong assumptions. Therefore, the limitations of these approaches should be taken into account when they are applied to disconnected networks.

For resource constraints and limited availability of the original guideline author, the update planned during EUnetHTA JA3 could not be implemented. Instead, a preliminary work on this topic has been engaged by EUnetHTA in 2020, in the format of a concept paper in which the needs for revision of a methodological guideline have been collected, broadly discussed and described.

**Table 2.1. Existing EUnetHTA documents**

| Title | Scope |
|---|---|
| Comparators & Comparisons: Direct and indirect comparisons (2015) [1] | *Methodological guideline*<br>To make the best use of available evidence on the efficacy of a treatment, it is common to combine results from several randomised controlled trials (RCTs) in a meta-analysis. This guideline focuses on the methods available for treatment comparisons. Their strengths and limitations are discussed and recommendations are provided in order to support Relative Effectiveness Assessors in their activity. The planning stages of a systematic review are not covered here. |
| Comparators & Comparisons: Direct and indirect comparisons - third edition (2020) [2] | *Concept paper on a methodological guideline*<br>Proposal to update the existing guideline based on the feedback received through different channels (e.g., survey of assessment teams, feedback form on the website, direct contact, and feedback from |

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|---|---|
| | industry), discussion with methodological experts, and through a review of peer-reviewed literature and relevant published methodological guidelines. |
| EUnetHTA SOP: Scoping, Developing 1st Draft of the Project Plan and Submission Dossier(OT) - OT-02-ScoDevDPPSubDos | |
| EUnetHTA SOP: Data Extraction (OT) - OT-03-DatExt | |
| EUnetHTA SOP: Internal Review of Submission Dossier - PT-02-IntRevSD | |
| EUnetHTA SOP: Scoping, Developing Project Plan - PT-02-ScopDevPP | |
| EUnetHTA SOP: Data Extraction (PT) - PT-03-DatExt | |
| SOP "How to Create and Maintain a Methodological Guideline" [3] | 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. |
| SOP "How to maintain a SOP" [4] | 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. |

Based on feedback provided in JA3, it is necessary to agree on main principles on how to deal in practice with indirect comparisons in reports (e.g. in which cases to present results or not, how to discuss/present the limitations).
In addition, including other existing methodologies in the EUnetHTA guideline "Comparators & Comparisons: Direct and indirect comparisons" was also identified as a need for indirect treatment comparisons (in particular methodologies for indirect treatment comparisons (ITC), like matching adjusted indirect comparison (MAIC) and simulated treatment comparison (STC)). The preliminary work engaged in 2020 will serve as a basis to update the guideline. At the beginning of the project, the hands-on team will discuss aspects that need consideration for this 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.

**D4.3.1:** To produce a practical guideline on how to deal in practice with indirect comparisons in reports (and which data/documents should then be requested from the HTD).

**D4.3.2:** To update of existing EUnetHTA guideline "Comparators & Comparisons: Direct and indirect comparisons".

**D4.3.3:** To check the existing EUnetHTA SOPs for consistency with the practical guideline and the updated EUnetHTA guideline on indirect comparisons; updates will be considered.

## *3.1 Methods to achieve the objectives*

**D4.3.1 – D4.3.2:** At the beginning of the project, the hands-on team will discuss aspects that need consideration for update of the EUnetHTA guideline "Comparators & Comparisons: Direct and indirect comparisons". In particular, the need for inclusion of other existing methodologies for indirect treatment comparisons was identified. The update will be based on the feedback received through different channels in JA3 (e.g. survey of assessment teams, feedback form on the website, direct contact, and feedback from HTD), discussion with methodological experts, and through a review of peer-reviewed literature and relevant published methodological guidelines. The preliminary work engaged in 2020 will

serve as a basis to update the guideline. Based on this work, a practical guideline on how to deal in practice with indirect comparisons in reports will be then developed. All processes will be compliant with the EUnetHTA SOP "How to Create and Maintain a Methodological Guideline".

**D4.3.3:** The existing EUnetHTA SOPs will be checked for consistency with the practical guideline and the updated EUnetHTA guideline on indirect comparisons. All processes will be compliant with the EUnetHTA SOP "How to Maintain an SOP".

### *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 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, the following hands-on groups will be kept informed: D4.2 on Scoping process, D4.4 on Endpoints, D4.5 on Applicability of evidence, D4.6 on Validity of clinical studies, D5.1 on JCA/CA Submission Dossier Template and D5.2 on JCA/CA Assessment Report Template.

## *4.2 Timelines*

**Table 4.1. Timetable**

| **Deliverable** | **D4.3.1 – Comparators and comparisons** | | **D4.3.2 – Direct and indirect comparisons** | |
|---|---|---|---|---|
| **Milestones** | Start date | End date | Start date | End date |
| **Project duration** | 25/02/2022 | 04/11/2022 | 28/09/2021 | 29/07/2022 |
| **1st Draft deliverable** | 25/02/2022 | 26/04/2022 | 28/09/2022 | 26/01/2022 |
| **Public consultation** | 01/08/2022 | 30/08/2022 | 02/05/2022 | 31/05/2022 |
| **Validate final version deliverable (CSCQ)** | 18/10/2022 | | 12/07/2022 | |
| **Endorsement final version deliverable (CEB)** | 02/11/2022 | | 27/07/2022 | |
| **Estimated finalisation date of the deliverable *** | 04/11/2022 | | 29/07/2022 | |

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

# 5 REFERENCES

1. EUnetHTA. Comparators & Comparisons: Direct and indirect comparisons. Methodological guideline. 2015.

2. EUnetHTA. Comparators & Comparisons: Direct and indirect comparisons. Concept paper on a methodological guideline. 2020.

3. EUnetHTA SOP: How to Create and Maintain a Methodological Guideline (2020)

4. EUnetHTA SOP: How to Maintain an SOP (updated 2019)