eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA 21

D5.2: Joint Clinical Assessment Report Template and Summary Template

Version 1.0, 17/04/2023

Document history and contributors

Version	Date	Description
0.1	22-11-2022	First draft
0.2	03-02-2023	Second draft
0.3	03-03-2023	For CSCQ validation
0.4	17-03-2023	For CEB endorsement & EC approval
1.0	17-04-2023	For publication

Disclaimer

Participants

Hands-on group	Haute Autorité de Santé (HAS), France Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG), Germany National Centre for Pharmacoeconomics (NCPE), Ireland Zorginstituut Nederland (ZIN), The Netherlands
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CEB	

The work in EUnetHTA 21 is a collaborative effort. While the agencies in the Hands-on Group actively wrote the deliverable, the entire EUnetHTA 21 consortium was involved in its production throughout various stages. This means that the Committee for Scientific Consistency and Quality (CSCQ) reviewed and discussed several drafts of the deliverable prior to validation. Afterwards the Consortium Executive Board (CEB) endorsed the final deliverable prior to publication.

Associated HTA bodies

The draft deliverable was reviewed by associated HTAb. The draft template was not open for public consultation, as the draft guidance on the JCA report template underwent public consultation between 01.08.2022 and 30.08.2022.

Associated HTA bodies who reviewed	Dachverband der Österreichischen Sozialversicherung, [DVSV], Austria Norwegian Institute of Public Health, [NIPH], Norway Health Information and Quality Authority [HIQA], Ireland Gesundheit Österreich GmbH [GÖG], Austria Swedish Agency for Health Technology Assessment and Assessment of Social Services, [SBU], Sweden Finnish Medicines Agency, [FIMEA], Finland Regione Emilia-Romagna, [RER], Italy The Public Agency of the Republic of Slovenia for Medicinal Products and Medical Devices, [JAZMP], Slovenia

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Instructions for use

Instructions to authors are presented in grey-shaded boxes. These boxes will be deleted in the final reports.

The template includes suggested standard text in plain lay-out wherever possible (to be expanded in later versions of the template). This aims to support the authors and the consistency of reports. However, this text can be edited by the authors as appropriate.

If any tables or sections are not applicable to the report (e.g., in case no data is submitted by the HTD), they can be deleted.

In the final template, table templates and instructions for use for the tables might be placed in an accompanying documents and table banks.

Also refer to the appropriate (methodological) guidelines which include detailed instructions and elements to report.

It is the responsibility of the HTD to provide the analysis needed for the assessor to robustly assess the information provided. It is not expected that any additional analysis would need to be undertaken by the assessment team.

The following guidelines should be taken into consideration when preparing the JCA report:

<List available guidelines>

List of abbreviations

The following list presents suggestions for abbreviations. It should be adapted to the report. Additional rows can be added to the table if necessary.

Abbreviation	Meaning
CEB	Consortium Executive Board
CSCQ	Committee for Scientific Consistency and Quality
CSR	Clinical Study Report
EU	European Union
HaDEA	European Health and Digital Executive Agency
HTA	Health Technology Assessment
HTAR	Regulation (EU) 2021/2282 of the European Parliament and of the Council on HTA assessment
HTD	Health Technology Developer
IVD	In vitro Diagnostic Medical Device
JCA	Joint Clinical Assessment
PICO	Population – Intervention – Comparator - Outcome
PT	Preferred Term
RCT	Randomized controlled Trial
RoB	Risk of Bias
SmPC	Summary of Product Characteristics
SOC	System Organ Class

Table of Contents

List of tables

1 General information on the joint clinical assessment

At the beginning of the report general information on the joint clinical assessment should be provided. This includes information on assessors and co-assessors, an overview of procedural steps and their dates as well as information on the involvement of stakeholders and external experts (patients, clinical experts and other relevant experts). Information on previous Joint Scientific Consultations should be provided.

1.1 Stakeholder and External Expert Involvement

Stakeholders were consulted early in the JCA scoping process to support the development of the PICO question(s)

Input from patients, clinical experts and other relevant experts were used to support the development of the PICO question(s)

Patients, clinical experts and other relevant experts were involved in the assessment process and answered specific questions from the Assessors/Co-assessors.

Table 1: Contributor Table

Contributor	**Patient or healthcare professional (HCP)**	**Organisation or individual**	**Type and timing of involvement**
Stakeholders	Patients and healthcare professionals	*<List all stakeholders/ organisations that participated in the JCA. They should be named on an individual level:>* *[name organisation], [abbreviation], [country]*	*< e.g. Participated in the open call for input during the scoping process. Completed an online submission>*
Expert	Clinical expert(s)	*<Before naming an expert, it should be confirmed the expert is in agreement with this>.* *[name individual], [organisations], [country]* *Or* *<a general description of the type of expert could be added, such as "clinical professional, working at a hospital in country X">*	*<e.g. Answered specific questions during the JCA, participated in meetings>*

	Patient(s)	*<Individual patients should not be named, due to legal constraints, but a general description could be provided>:* *[e.g. select one or modify descriptions: Patient living with the condition; carer – parent of a child living with the condition;], [country]*	*[e.g. Participated in an interview during the scoping process; participated in the scoping meeting]*
	Other relevant expert(s)	*Before naming an expert, it should be confirmed the expert is in agreement with this>.* *[name individual], [organisations], [country]* *Or* *<a general description of the type of expert could be added, such as "Expert on the type of health technology under assessment or issues relating to clinical study design >*	
footnotes (please delete this line if it is not needed)			
HCP: Health Care Professional; JCA: Joint Clinical Assessment			

Stakeholder organisations were invited to provide input via an online questionnaire during the scoping process. (Insert number) stakeholder organisation(s) made submissions. Stakeholder organisations represented (healthcare professionals working in the therapeutic area of (insert health condition) and/or (patients with (insert health condition). Stakeholder organisations were European (insert number) and/or national (insert number).

Patients and clinical experts were recruited via (insert name of organisation) and/or a public call for involvement. Other relevant experts were recruited via (*complete as appropriate*)

(Insert number) patient(s) acting as (an) external expert(s) were involved. The (majority of) patients had collective knowledge on the disease and/or experiences with the technology under evaluation (either self or knowledge obtained from other patients).

If relevant, comment on geographical representation of patients

(Insert number) clinical expert(s) were involved. The (majority of) clinical expert(s) had clinical experience with the disease and/or clinical experience with the technology under evaluation.

If relevant, comment on geographical representation of clinical experts

All patients, clinical experts and other relevant experts were free from conflict of interests

Submissions from stakeholder organisations, including details of the organisations funding, are published alongside the JCA report (link)

Input from external experts obtained via Expert Input Templates is published in Appendix A.

2 Background

2.1 Overview of the health condition

Here a brief summary of the health condition should be given, including the prevalence or incidence of the health condition in Europe (countries in which the HTAR is in effect). Also, briefly describe the target population and its characteristics. Specific characteristics that differentiate between (sub)populations reflected in the assessment scope are to be described.

2.2 Characterisation of the health technology

2.2.1 Characteristics of the health technology

The characteristics of the medicinal product under assessment are presented in the following table.

Additional rows with relevant information can be added to the table if necessary.

Table 2: Characteristics of the health technology (medicinal product)

Proprietary name	
Active substance(s)	
Pharmaceutical formulation(s)	
Indication	<indication relevant for submission>
Marketing authorisation holder	
Mechanism of action	<First paragraph in section 5.1 of the SmPC. Summarise if necessary>
ATC code	
footnotes (please delete this line if it is not needed)	
ATC: Anatomical Therapeutic Chemical / Defined Daily Dose Classification; SmPC: Summary of Product Characteristics	

Alternative in case of medical device / IVD.

The characteristics of the medical device under assessment are presented in the following table.

Additional rows with relevant information can be added to the table if necessary.

Table 3: Characteristics of the health technology (medical devices (including IVDs))

Device trade name(s)	
Name of manufacturer	
Device description according to the European Medical Device Nomenclature (EMDN)	
Risk class of device	
Function of the device	[For MDs: therapeutic, disability compensation, other For IVDs: screening, monitoring, diagnosis or aid to diagnosis, prognosis, prediction, companion diagnostic]
Model(s) of the device/ reference number(s)/ Software version	
Intended purpose of the device	[Sourced from the SSCP or IFU. Summarise if necessary]
Indication(s) and target population(s)	[Sourced from the SSCP or IFU. Summarise if necessary]
Contraindications and/or restrictions for use and/or limitations of the device	[Sourced from the SSCP or IFU. Summarise if necessary]
Description of the device including its constituents	[Sourced from the SSCP or IFU. Summarise if necessary]
Mode(s) of action (MDs) or test principle (IVDs)	[Sourced from the SSCP or IFU. Summarise if necessary]
If applicable, specific description for the connected technology	
For medical devices with an embedded decision-making system based on machine learning processes (technologies falling within the scope of artificial intelligence): description of the functions built or evolving using these technologies	
footnotes (please delete this line if it is not needed)	
EMDN: the European Medical Device Nomenclature; *IFU: Instruction for Use;* IVD: in vitro diagnostic; MD: medical device, *SSCP: Summary of Safety and Clinical Performance*	

2.2.2 Requirements/instructions for use

Details on the administration and dosing of the medicinal product under assessment are described in the following table.

Additional rows with relevant information can be added to the table if necessary.

Table 4: Administration and dosing of the health technology (medicinal product)

Method of administration	
Doses and dosing frequency	
Duration of treatment (including end of treatment criteria if necessary)	
footnotes (please delete this line if it is not needed)	
abbreviations (please delete this line if it is not needed)	

Alternative in case of medical device / IVD.

The characteristics of use for the medical device/ IVD under assessment are described in the following table.

Additional rows with relevant information can be added to the table if necessary.

Table 5: Characteristics of use (by (sub)population or patient group if appropriate) (medical devices (including IVDs))

Specific intended use of the device if relevant	[Examples (can be deleted as appropriate) to administer and/or remove a medicinal product to act as a companion diagnostic to emit hazardous, or potentially hazardous, levels of ionising and/or nonionising radiation to be operated together with other devices or products]
Description of (surgical) procedures, services and organisational aspects associated with the use of the device	
Suggested profile and training for users as outlined in the SSCP or IFU	
MRI compatibility	
footnotes (please delete this line if it is not needed)	
IFU: Instructions for Use; MRI: magnetic resonance imaging; SSCP_ Summary of Safety and Clinical Performance	

2.2.3 Regulatory status of the technology

Regulatory information on the medicinal product under assessment is provided in the following table.

Table 6: Regulatory information on the health technology (medicinal product)

Orphan medicinal product (yes/no)	
Conditional marketing authorisation (yes/no)	
Specific obligations of the conditional Marketing Authorisation	e.g. safety monitoring; additional efficacy information*. [if necessary, please provide additional information in the text]
Exceptional circumstances (yes/no)	
ATMP (yes/no)	
PRIME (yes/no)	
First indication (yes/no)	[If no, please provide a link to the SmPC in the text]
Details of ongoing early access programs in the EU (as provided by the MAH)[a]	[List countries only]
a: for further details on ongoing early access programs please refer to the submission dossier	
ATMP: Advanced Therapy Medicinal Products; MAH: marketing authorization holder; *SmPC: Summary of Product Characteristics*	

Details of other licensed indications are available from the SmPC <insert link>

Further regulatory information is included in the submission dossier <insert link|>.

Alternative in case of medical device / IVD.

Regulatory information on the medical device/ IVD under assessment is provided in the following table.

Table 7: Regulatory information on the health technology (medical devices (including IVDs))

Basic unique device identification-device identifier (UDI-DI)	
Name, identification number and country of Notified Body	
Date of initial CE marking	
Expiry date of current certificate	
Date and reference of the expert panel opinion (MD) or expert panel view (IVD)	
footnotes (please delete this line if it is not needed)	
IVD: in vitro diagnostic; MD: medical device; UDI-DI: Unique Device Identification-Device Identifier	

Further regulatory information is included in the submission dossier (insert link).

3 Research question and scope

The JCA should be performed against the chosen parameters which are based on the assessment scope. The assessment scope was identified through a survey of Member States, a consolidation process and subsequent endorsement by the HTA Coordination Group.

The consolidated assessment scope is presented in the following table.

In case of cells with exactly matching content, please write 'The same as for PICO x'. In cases where the HTD could choose a comparator therapy from several options, the respective choice of the HTD is printed in **bold**. This should be explained in a footnote. All outcomes (including outcome measures as appropriate) should be listed once under O for all PICO question(s)).

Table 8: Assessment scope including the consolidated PICO questions

Description of PICO elements	**PICO 1**	**PICO 2**	**PICO 3**
P			
I			
C[a]			
O	The following outcomes are assessed across all PICO question(s) <list outcomes>		
a: In cases where the HTD could choose a comparator therapy from several options, the respective choice of the HTD is printed in **bold**.			
PICO: population-intervention-comparator-outcome			

4 Results

The results section presents the findings of the systematic information retrieval, the included studies and the data on relative effectiveness and relative safety according to the PICO question(s).

The assessment is based on the submission dossier with the CSR being the primary data source (where available). Discordant results across data source may be discussed if relevant.

The results sections will provide an assessment of the methods used by the HTD in the submission dossier, as appropriate. In addition, the degree of certainty of the relative effects, taking into account the strengths and limitations of the available evidence will be described. The report shall not contain any value judgement or conclusions on the overall clinical added value of the assessed health technology and shall be limited to a description of the scientific analysis.The assessment will be done in conformity with the existing methodological guidelines in place at the time of assessment.

The results section should also describe when relevant information is missing.

The results section provides the findings of the systematic information retrieval, characterises the included studies and presents the results on relative effectiveness and relative safety of the health technology under assessment versus the comparators defined in the PICO question(s). Factors which may affect the certainty of the relative effects are identified, taking into account the strengths and limitations of the available evidence.

4.1 Information retrieval

The description of the information retrieval review should include, at a minimum, the appropriateness of sources and search strategies and whether all relevant studies were identified and included by the HTD.

An assessment of the appropriateness of the sources and the search strategies is provided in Appendix BB. The studies included in the assessment were compiled using the following information:

Sources provided by the HTD in the dossier:

- list of HTD sponsored studies on <health technology assessment> (as of DD/MM/YYYY)
- bibliographic search for <health technology under assessment> (last search on DD/MM/YYYY)
- bibliographic search for <comparator(s)> (if applicable, last search on DD/MM/YYYY)
- search in study registers / study result databases for <health technology under assessment> (last search on DD/MM/YYYY)

- search in study registers / study result databases for <comparator(s)> (if applicable, last search on DD/MM/YYYY)

The approach to verifying the completeness of the included studies is still under discussion. A robust process for scientific completeness needs to be in place and will be developed.

No additional relevant study was identified through the check for completeness. / The check for completeness identified (an) additional relevant study/studies.

In case additional studies were identified, a description of these studies and the consequences for the assessment should be provided.

Resulting list of included studies: overall and by PICO question

An overview of all included studies and all associated references for these studies overall and per PICO question should be provided.

The following table lists the studies used for the assessment including the available documentation and identifies which studies are relevant for the PICO questions of the assessment, respectively.

Please add a row above each (set of) studies indicating whether they provide direct or indirect evidence to address the PICO question. Please also add the comparison under evaluation. Please add the study acronyms in bold in the first row in addition to the study ID, the study design and the study intervention and comparator. Add footnotes to provide details. All studies addressing the scope should be included in this table, If the HTD did not provide evidence for a specific PICO in the assessment scope, "No evidence provided by the HTD" should be recorded under the relevant PICO heading.

Table 9: Included studies – list of relevant studies used for the assessment

Study reference/ID **Study type** **Study interventions**	**Study for marketing authorization / CE marking of the technology under assessment***	**Sponsored[a] or third-party study of the technology under assessment**	**Available documentation from the submission dossier**
PICO 1			
Studies providing direct evidence [intervention] vs. [comparator]			
Study ID (**Acronym**[b]) *e.g. RCT/ cohort study* study intervention vs. comparator	yes/no	Sponsored / not sponsored	• CSR: [ref] • Registry entry[c]: [ref] • Publication or other reference: [ref]
Study ID (**Acronym**[b]) *e.g. RCT/ cohort study* study intervention vs. comparator	yes/no	sponsored / not sponsored	• CSR: [ref] • Registry entry[c]: [ref] • Publication or other reference: [ref]
etc			
PICO x			
Studies providing indirect evidence [intervention] vs. [comparator]			
Study ID (**Acronym**[b]) *e.g. RCT/ cohort study* study intervention vs. comparator	yes/no	Sponsored / not sponsored	• CSR: [ref] • Registry entry[c]: [ref] • Publication or other reference: [ref]
etc			
* if yes, please provide information such as date and commission implementing decision in footnote a: study sponsored by the HTD or in which the HTD participated financially in some other way b: in the following tables, the study is referred to with this abbreviated form c: study registry entry, number (NCT-Number, EudraCT-Number)			
CSR: clinical study report; HTD: health technology developer; RCT: randomized controlled trial			

In case any studies included by the HTD have been excluded from the assessment, these should be listed and a reason for exclusion should be provided. If no study has been excluded this text and table can be deleted.

The following table lists studies which have been included by the HTD in the submission dossier but which were not considered relevant for the assessment.

Table 10: List of excluded studies – studies included by the HTD but not used in the assessment

Study reference/ID	**Reason for exclusion**
<study 1>	
<study 2>	
footnotes (please delete this line if it is not needed)	
HTD: health technology developer	

4.2 Characteristics of included studies

Study design and study populations

Information on the study type and design (please refer to the appropriate guidelines), and on enrolled study populations (e.g. diagnosis, general severity of disease, line of therapy) should be provided. The study interventions should be characterised and information on the course of the study (e.g., planned and actual follow-up times per outcome) should be presented.

The following table characterises the studies included in the assessment.

Instructions to authors for the table

Study arms: Group = name of the intervention; include dosing, posology etc only if necessary to identify the relevant treatment arms for the assessment (e.g. those with finally approved dosing when additional arms used doses which finally were not approved).

Study duration: Including screening, treatment, and follow-up as appropriate

Data cut-off: specify whether they were preplanned, and for unplanned specify what motivated the interim analyses.

Study endpoints Primary: primary endpoint of the study; key secondary: only secondary endpoints controlled for multiplicity; other: only if included in the PICO question.

Table 11: Characteristics of the included studies

Study reference/ID	**Study type and design**	**Study population**	**Study arms (number of randomized/included patients)**	**Study duration, data cut off(s) and locations**	**Study endpoints**
<study 1>	*RCT,* *blind/open, parallel/cross-over, etc.*	*relevant characteristics, e.g. degree of severity including respective key inclusion/exclusion factors in footnotes*	*Group 1 (N = XX)* *Group 2 (N = XX)* *Group 3 (N = XX)*	• *Study duration:* • *Completion date (estimated, if study is ongoing): XX XX 20XX* • *1. Data cut-off: XX XX 20XX (planned interim analysis)* • *2. Data cut-off: XX XX 20XX (requested by EMA; not planned)* *(if complex can be described in separate paragraph)* • *Number of centres by continent*	*Primary:* *Key secondary*[a]*:* Other[b]: *(if complex can be described in separate paragraph)*
a: only secondary endpoints controlled for multiplicity b: only if included in at least one PICO					
N: number of included patients; RCT: randomized controlled trial;					

The following table describes the interventions in the included studies.

Table 12: Characterisation of the interventions of included studies

Study reference/ID	Study intervention	Study comparator
Study XXX	*e.g. 250 µg, 1 Inhalation bid + Placebo 2 Inhalations bid*	*e.g.200 µg, 2 Inhalations bid + Placebo 1 Inhalation bid*
	<Optional additional content with treatment characteristics e.g. pre-treatment, treatment during the run-in phase, concomitant/prohibited medications as required>	
footnotes (please delete this line if it is not needed)		
abbreviations (please delete this line if it is not needed)		

If the table characterising the interventions of the included studies in detail is very lengthy, e.g. due to a larger number of studies, it can be shifted to an appendix. If the table is provided in the appendix of the report, include a reference to this table at this point.

The next table provides information on treatment duration and observations periods in the included studies.

Table 13: Information on the course of included studies (including planned duration of follow-up)

Study reference / ID Outcome category	Planned follow-up	Study intervention	Relevant comparator
<Study 1>		**N =**	**N =**
Treatment duration [<month/weeks>] Median [Min; Max] Mean (SD)	 – –		
Observation period [<months/weeks>] <outcome> Median [Min; Max] Mean (SD) <outcome>	 <Until disease progression/x days after end of treatment, …> – – <Until disease progression/x days after end of treatment, …>		
<Study 2>		**N =**	**N =**
<.....>			
footnotes (please delete this line if it is not needed)			
N: number of randomized patients; SD: standard deviation			

4.3 Study results on relative effectiveness and relative safety

The results on relative effectiveness and relative safety should be presented by PICO question. All PICO question(s) relevant for a specific patient population should be clustered in one chapter. The relative effects versus each relevant comparator should then be assessed sequentially.

4.3.1 Results for patient population < x>

At the beginning of the section for a given patient population a table with references to the included studies enrolling this population should be provided.

If a subpopulation of the study is analysed for the assessment, the characteristics of the relevant subpopulation should be described and the number of included patients should be provided.

The following table describes the studies that are included in the assessment for patient population <x> and specifies for each study, if the complete study population or a relevant subpopulation is used, respectively.

Table 14: Studies included in the assessment of patient population <x> including analysed populations

Study reference/ID **Relevant study arms (number of randomized/included patients)**	**Analysed population (number of randomized/included patients)**
PICO <X>	
<type of comparison>: <XXX> vs. <YYY>	
<study x> *<Group 1> (N = XX)* *<Group 2> (N = XX)*	*<characteristics x/y/z (if applicable)>* *Complete study population / relevant subpopulation[a]* *<Group 1> (n = XX)* *<Group 2> (n = XX)*
<study 1> *<Group 1> (N = XX)* *<Group 2> (N = XX)*	*Complete study population*
<study 2> *<Group 1> (N = XX)* *<Group 2> (N = XX)*	*<characteristics x/y/z>* *Relevant subpopulation[a]:* *<Group 1> (n = XX)* *<Group 2> (n = XX)*
a: In the case that a subpopulation of the study is analysed for the assessment, specify the number of included patients and describe the characteristics of the relevant subpopulation.	
N: number of randomized patients ; n: number of patients	

Comment on factors related to the population and comparator which may affect the certainty of the evidence, in line with the available guidelines. This requires consideration of a potential mismatch between the PICO defined in the assessment scope and the population and/or comparators defined in the studies (i.e applicability) included in the assessment, among other potential sources of uncertainty.

4.3.1.1 Patient characteristics

Patient characteristics

The baseline demographics (e.g. age and sex) and disease characteristics (e.g. duration and severity) of the patients enrolled in the included studies should be presented in tables. In case relevant characteristics are missing, please add them in or below the table with “no data”. The reporting of standardized differences is not necessary for RCTs, but must be reported for non-

randomised studies. Where differences were observed between treatment groups in RCTs this should be described in the text below Table 14. In case of an indirect comparison based on non-randomized evidence (e.g., an external comparison between a single-arm trial and another source of data), if a causal inference method has been applied to adjust for confounding (such as propensity scores), baseline characteristics should be reported before and after adjustment with corresponding standardized differences (before and after adjustment). Refer to the relevant guidelines for further information. The comparability of patient characteristics between treatment groups in the included studies and between studies should be reported. Comment on the potential for any differences in patient characteristics, within or between studies, to affect the certainty of the results.

The following table provides the characteristics of the patients in the studies included in the assessment of <patient population>.

Table 15: Patient baseline characteristics including treatment / study discontinuations for population <x>

Study reference / ID Characteristics Category	**Study intervention**	**Relevant comparator**	**Standardized difference (if applicable)**
<Study 1>	*<intervention>* *N =*	*<comparator>* *N =*	
Age [years], mean (SD) *Sex [f / m], %* *<more characteristics>, n (%)* *<Category 1>* *<Category 2>* *<Category 3>* ...			
Treatment discontinuation, n (%) *Study discontinuation, n (%)*			
<Study 2>	*<intervention>* *N =*	*<comparator>* *N =*	
...			
footnotes (please delete this line if it is not needed)			
f: female; m: male; n: number of patients in the category, N: number of randomized patients; ND: no data;; RCT: randomized controlled trial; SD: standard deviation			

There were no major differences between the treatment groups in the included studies with the following exceptions:

4.3.1.2 Outcomes for PICO <x-1>

The section presents the results on relative effectiveness and relative safety for a given PICO question. An overview of the availability of evidence for the PICO question(s), by e.g. listing the included studies relevant for PICO <x-1>, should be provided. Outcomes and their measurement instruments should be discussed in line with the relevant guidelines. The approach to the comparison (e.g. direct comparison within RCT, indirect comparison of RCTs etc.) should be briefly outlined. A more detailed description of the evidence synthesis methods, together with the associated strengths and limitations, should be discussed under the heading "Evidence synthesis analysis methods".

Available outcomes

A list of all relevant outcomes for PICO <x-1> available in the included studies should be provided. When an outcome in the PICO question is not included in the assessment, the reasons should be stated. Indicate whether the outcomes requested by Member States align with the data? provided by the HTD. Comment on factors related to the outcomes which may affect the certainty of the evidence, in line with the available guidelines. This requires consideration of a potential mismatch between the PICO defined in the assessment scope and the outcomes defined in the studies included in the assessment, among other potential sources of uncertainty.

Data for the individual outcomes should be presented and described briefly.

The following table provides an overview of the outcomes available in the studies included in the assessment of PICO <x-1>.

Table 16: Matrix of outcomes in the included RCTs for PICO <x-1> - direct comparison: <intervention> vs. <PICO comparator>

Outcomes	**Study reference/ID**		
	<study 1>	<study 2>	<study 3>
<outcome 1>, <OMI if applicable>	*<yes/no>*	*<yes/no>*	*<yes/no>*
<outcome 2>, <OMI if applicable>			
<outcome 3> , <OMI if applicable>			
<outcome 4> , <OMI if applicable>			
footnotes (please delete this line if it is not needed) OMI: Outcome Measurement Instrument			

Table 17: Matrix of outcomes in the included studies for PICO <x-1> - indirect comparison: <intervention> vs. <PICO comparator>

Outcomes	**Comparison Study reference/ID**				**Indirect comparison method**
	<intervention> vs. <common comparator>		**<PICO comparator> vs. <common comparator>**		
	<study 1>	<study 2>	<study 3>	<study 4>	
<outcome 1>, <OMI if applicable>	*<yes/no>*	*<yes/no>*	*<yes/no>*	*<yes/no>*	E.g. Bucher ITC, NMA, MAIC (anchored/unanchored), N/A
<outcome 2>, <OMI if applicable>					
<outcome 3>, <OMI if applicable>					
<outcome 4>, <OMI if applicable>					
footnotes (please delete this line if it is not needed) OMI: outcome measure instrument					

Risk of bias of the original clinical studies

For the assessment of RoB for different study types, refer to the relevant guidelines. Outcomes with similar risk of bias results can be grouped if the arguments/reasons for putting a "Some concerns" or "High" for a particular risk of bias is the same. However, if the randomisation process was biased for other reasons in study A than in B and both deserve a "Some concerns" or "High", this should be presented in two separate lines because we do need to know that it was for different reasons (and report the reasons). If necessary, detailed reports of those assessments can be placed in an appendix. Please provide reasons for judgements in a comment.

RoB assessment is not required for uncontrolled trials (single-arm trial), cross-sectional studies and case series(report) as they are inherently at high risk of bias.

The RoB of any evidence synthesis study needs to be assessed separately. Please refer to the appropriate guidelines.

Table 18: Risk of bias (RCT at study outcome level (Cochrane RoB 2.0)

Domain	**Bias arising from randomization process**	**Bias due to deviations from intended interventions**	**Bias due to missing outcome data**	**Bias in measurement of the outcome**	**Bias in selection of the reported result**	**Overall risk of bias**	**Comments**
Study / Outcome	Low / Some concerns / High	Low / Some concerns / High	Low / Some concerns / High	Low / Some concerns / High	Low / Some concerns / High	Low / Some concerns / High	
footnotes (please delete this line if it is not needed)							
abbreviations (please delete this line if it is not needed)							

Table 19: Risk of bias (non-randomised studies other than uncontrolled trials, cross-sectional studies and case series (report)) at outcome level (Cochrane ROBINS-I)

Domain	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias	Comments
Study / Outcome	Low / Moderate / Serious / Critical / NI	Low / Moderate / Serious / Critical / NI	Low / Moderate / Serious / Critical / NI	Low / Moderate / Serious / Critical / NI	Low / Moderate / Serious / Critical / NI	Low / Moderate / Serious / Critical / NI	Low / Moderate / Serious / Critical / NI	Low / Moderate / Serious / Critical / NI	
footnotes (please delete this line if it is not needed)									
NI: No information									

Evidence synthesis methods

Briefly describe the evidence synthesis methods used, including the associated strengths and limitations, and any factors arising from these methods and their application which may affect the certainty of the evidence, in line with the available guidelines.

Health outcome results

The relative effects of the health technology versus the comparator should be described including relevant sensitivity analyses and supplementary analyses, in line with the relevant guidelines. The description should address any issues affecting the degree of certainty of the relative effects including ROB at the outcome level.

In case insufficient evidence is provided by the HTD, this will be described.

Guidance to authors for all results tables:

In case pooled data is included, please add the p-value for heterogeneity (p_H) as well as the I^2 and present the corresponding forest plots in appendix B2 (additional study results).

In case any time-to-event analysis is presented, please provide appropriate graphs of the function.

Refer to the relevant guidelines for guidance on reporting of the results Where appropriate, Table 20, Table 21 and Table 22 can be adjusted to report different population-level summary measures and/or effect measures (e.g., median and inter-quartile range instead of mean and standard deviation, odds ratios instead of risk-ratios) The format for Table 21 can be adjusted in situations where fractional polynomial meta-analysis has been carried out, or other non-

proportional hazards methods have been used. When appropriate, reporting of p-value must also include margin(s) of non-inferiority or equivalence.

For Table 20, Table 21 and Table 22, please consider the following questions and use the appropriate abbreviations to fill in the columns on "hypothesis testing":

1. Is the test significant against the specified alpha-level in the SAP of the corresponding study? (S = statistically significant, NS =non-significant, NO = "nominal" p-value (no alpha-level was specified a priori))

2. Was the test prespecified according to the SAP of the corresponding study? (P = prespecified, NP = not prespecified)

3. Was the test controlled for multiplicity? (C = controlled, NC = not controlled).

Table 20: Relative effectiveness results (dichotomous outcomes) – direct comparison: <intervention> vs. <comparator>

Time point	**<Intervention>**		**<Comparator>**		**<Intervention> vs. <Comparator>**			
Outcome Study reference/ID	**N**	**Patients with event n (%)**	**N**	**Patients with events n (%)**	**[e.g. RR] [95 % - CI] p-value**	**Hypothesis testing**	**RD [95 % -CI] p-value**	**Hypothesis testing**
<time point>								
<outcome 1> <study XXX> <study XXX> Total[x] (p_H = <XXX>; I^2 = <YYY>)						<1> - <2> - <3>		
<outcome 2> <study XXX> <study XXX> Total[x] (p_H = <XXX>; I^2 = <YYY>)								
Reading the "Hypothesis testing" columns: 1. Statistical significance: S = Satistically significant against the alpha level specified in the statistical analysis plan of the corresponding study, NS = Non-significant, NO = Nomimal p-value 2. Prespecification: P = Statistical test was prespecified according to the statistical analysis plan of the corresponding study, NP = Not prespecified 3. Multiple hypothesis testing. C = Appropriate control for multiplicity according to the statistical analysis plan and clinical study report of the corresponding study, NC = Not controlled								
x: calculated from meta-analysis								
CI: confidence interval, NI: No information, p_H: p-value from test for heterogeneity <specify>, RD: risk difference, RR. Relative risk								

Table 21: Relative effectiveness results (time to event outcomes) – direct comparison: <intervention> vs. <comparator>

Time point	**<Intervention>**		**<Comparator>**		**<Intervention> vs. <Comparator>**			
Outcome Study reference/ID	**N**	**Median time to event in <weeks/months> [95 % -CI] patients with event n (%)**	**N**	**Median time to event in <weeks/months> [95 % -CI] patients with event n (%)**	**HR [95 % -CI] p-values**	**Hypothesis testing**	**<add appropriate absolute difference> p-value**	**Hypothesis testing**
<time point>								
Overall Survival								
<study XXX>						<1> - <2> - <3>		
<study XXX>								
Total[x] (p_H = <XXX>; I^2 = <YYY>)								
<outcome 2>								
<study XXX>								
<study XXX>								
Total[x] (p_H = <XXX>; I^2 = <YYY>)								
Reading the "Hypothesis testing" columns: 1. Statistical significance: S = Satistically significant against the alpha level specified in the statistical analysis plan of the corresponding study, NS = Non-significant, NO = Nomimal p-value 2. Prespecification: P = Statistical test was prespecified according to the statistical analysis plan of the corresponding study, NP = Not prespecified 3. Multiple hypothesis testing. C = Appropriate control for multiplicity according to the statistical analysis plan and clinical study report of the corresponding study, NC = Not controlled								
x: calculated from meta-analysis								
CI: confidence interval, HR: hazard ratio, NI: No information, p_H: p-value from test for heterogeneity <specify>								

Table 22: Relative effectiveness results (quantitative outcomes) – direct comparison: <intervention> vs. <comparator>

Time point	**<Intervention>**			**<Comparator>**			**<Intervention> vs. <Comparator>**	
Outcome Study reference/ID	**N**	**Values at baseline mean (SD)**	**Change/values at <time> mean] (SD)**	**N**	**Values at baseline mean (SD)**	**Change/values at <time> mean (SD)**	**<effect> [95 % -CI] p-value**	**Hypothesis testing**
<time point>								
<outcome 1>								
<study XXX>								<1> - <2> - <3>
<study XXX>								
Total[x] (p_H = <XXX>; I^2 = <YYY>)								
<outcome 2>								
<study XXX>								
<study XXX>								
Total[x] (p_H = <XXX>; I^2 = <YYY>)								
Reading the "Hypothesis testing" columns: 1. Statistical significance: S = Satistically significant against the alpha level specified in the statistical analysis plan of the corresponding study, NS = Non-significant, NO = Nomimal p-value 2. Prespecification: P = Statistical test was prespecified according to the statistical analysis plan of the corresponding study, NP = Not prespecified 3. Multiple hypothesis testing. C = Appropriate control for multiplicity according to the statistical analysis plan and clinical study report of the corresponding study, NC = Not controlled								
x: calculated from meta-analysis								
CI: confidence interval, NI: No information, p_H: p-value from test for heterogeneity <specify>, SD: standard deviation								

Table 23: Safety outcomes for PICO 1

Time point	**<Intervention>**		**<Comparator>**	
Outcome Study reference/ID	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**
<time point>				
At least one adverse event <study XXX> <study XXX>				
Serious adverse events <study XXX> <study XXX>				
Severe adverse events [insert used scale] <study XXX> Grade ≥ 3 Grade 3 Grade 4 Grade 5 <study XXX> Grade ≥ 3 Grade 3 Grade 4 Grade 5				
Treatment discontinuation due to adverse events <study XXX> <study XXX>				
Treatment interruption due to adverse events <study XXX> <study XXX>				
Suspected unexpected serious adverse reaction <study XXX> <study XXX>				
Specific adverse event A[b] <study XXX> <study XXX>				
Specific adverse event B[b] <study XXX> <study XXX>				
a: calculated from meta-analyses b: As requested by member state(s) in their PICOs				
AE: adverse event; N: number of randomized patients; n: number of patients with event; PICO: Population – Intervention – Comparator – Outcome; SAE: serious adverse event				

Summary table including uncertainties of the evidence

Briefly summarise factors that affect the certainty of the evidence for PICO <x-1> in the following table. The table should only summarise factors which have already been described in

detail in the preceding sections of the report. No new information should be presented in this table.

Factors should be summarised in relation to the overall body of evidence i.e. both the original clinical studies and in relation to the evidence-synthesis analysis, if applicable. Refer to the relevant guidelines for further guidance. General factors which relate to all outcomes should be listed first in the table, followed by outcome-specific factors.

Relevant issues that should be discussed in the table are as follows:

Internal validity: Internal validity of individual clinical studies describes the risk of bias; instruments to be used for different study types are specified in the relevant guidelines. In the case of uncontrolled trials (e.g. single-arm trials), RoB assessment is not required. In the case of evidence synthesis, violations of the underlying assumptions should be described if the likely result is bias. For example, for indirect comparisons based upon disconnected evidence networks (e.g. synthesis of a single armed trial and another study), issues affecting internal validity of the indirect comparison (e.g. bias due to factors such as unmeasured confounding) should be listed.
Applicability: applicability describes the extent to which the PICO of the included studies matchess the PICO of the assessment

In the case of (network) meta-analysis, the relevance of the overall study pool and pooled effect estimates to the PICO must be considered. Consideration should also be given to the relevance of the target estimand(s) to the PICO question. For example, in a non-randomised study in which treated patients are matched with patients in a control group (e.g. using propensity scores), the 'average treatment effect in the treated' may be reported in a situation where the 'average treatment effect in the control' matches the population of the PICO more closely. Where evidence synthesis has been carried out inappropriately, resulting in an uninterpretable or irrelevant estimand (e.g. when the exchangeability assumption is violated), this should also be highlighted.

Heterogeneity and inconsistency: describes heterogeneity between different individual clinical studies for a given PICO. In the case of network meta-analysis, describe inconsistency where relevant. Results of both qualitative and quantitative assessment of heterogeneity should be reported, if relevant.

Other: Examples include publication bias; reporting bias; multiplicity; inappropriate inclusion or exclusion of studies from meta-analysis; (lack of) dose-response relationship when such a relationship would be expected; or any other methodological issues.

The table should not contain any new information, the content of the table should be referenced back to the particular section in the report for information of details.

The description of the effect estimate should include the point estimate and a measure of dispersion. In addition, the p-value should be provided. In the case of random-effects (network)

meta-analysis, results should include prediction intervals and heterogeneity estimates (see D4.3.1).

Table 24: Uncertainties of the evidence for <PICO 1>

Outcome	Design	Factors that may affect certainty of evidence	Effect estimate p-value[a]
All outcomes	<design, number of studies>	Discuss the factors that may affect certainty of evidence across all outcomes which may include: • Internal validity of individual studies and evidence synthesis • Applicability • Heterogeneity and Inconsistency • Other	N/A
<outcome>		Discuss the factors that may affect certainty of evidence for specific outcomes, as above.	
a: Use of an * indicates statistical significance versus a pre-specified alpha-level, use of a # indicates a pre-specified analysis according to the SAP (for individual studies) or evidence synthesis protocol, use of a $ indicates control for multiplicity. Alternatively indicate if no formal hypothesis testing was carried out			
abbreviations (this line can be deleted if it is not needed)			

A version of this table using categories according to the partial use of GRADE [insert reference to "Partial Use of GRADE in EUnetHTA Framework] is provided in Appendix D.

4.3.1.3 Outcomes for PICO <x-2>

The same as for preceding PICO question.

4.3.2 Results for patient population < y>

the same as for preceding patient population

4.3.2.1 Patient characteristics

4.3.2.2 Outcomes for PICO <y-1>

4.3.2.3 Outcomes for PICO <y-2>

4.3.3 Results of the main study from the clinical development programme of the intervention under assessment

If the results of the main studies (e.g. pivotal study) in the clinical development programme are not addressed by any of the PICOs those can be presented in this section.

Otherwise this section will be deleted from the assessment report.

For the presentation of information on the main study/studies the table templates for the sections above might be used.

Characteristics of the pivotal study

Patient characteristics

Outcomes of the pivotal study

5 References

6 Summary report

The summary report should present an independently readable overview of the assessment. It should include

- Background information with, as a minimum a description of the intervention and health condition to be treated
- State if stakeholders and/or external experts were involved
- Objective and scope (PICOs)
- Summary tables including uncertainties of the evidence for each PICO question (these tables can be extracted from the main report)

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Appendix A Input from external experts

Input from external experts obtained via the Expert Input Templates should be included in this appendix.

Appendix B Assessment of information retrieval

The approach to verifying the completeness of the included studies is still under discussion. A robust process for scientific completeness needs to be in place and will be developed.

Appendix C Additional study information and data

C.1 Additional characteristics of included studies

This appendix can contain the following information, if applicable (it can be deleted, if no additional characteristics of the included studies will be presented):

- in case that the table characterising the interventions of the included studies is very lengthy it can be displayed here instead of in the main text.

- if the RoB assessment of the included studies is very detailed, it can be reported here

C.2 Additional study results

This appendix can contain additional results not included in the main report, if applicable (it can be deleted, if no additional study results will be presented), for example:

- if meta-analyses are provided, the corresponding forest plots will be presented here.

- if Kaplan-Meier Plots are available, they will be presented in this appendix

C.3 Safety

This appendix will contain the following information on safety outcomes:

- summary data for safety outcomes including effect estimates

- tables for adverse events (all), adverse events (serious) and discontinuation due to adverse events each including effect estimates – disaggregated by System Organ Class (SOC) and Preferred Term (PT)

C.3.1 Safety outcomes including effect estimates

In the following table pre-specified analyses including information on control for multiplicity in any will be identified by footnotes. The analysis presented below are not pre-specified nor controlled for multiplicity unless explicitly identified by footnotes.

Table 25 Safety outcomes including effect estimates

Time point	**<Intervention>**		**<Comparator>**		**<Intervention> vs. <Comparator>**	
Outcome Study reference/ID	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95 % -CI]**	**RD [95 % -CI]**
<time point>						
At least one adverse event <study XXX> <study XXX> Total[a] (p_H = <XXX>; I^2 = <YYY>)						
Serious adverse events <study XXX> <study XXX> Total[a] (p_H = <XXX>; I^2 = <YYY>)						
Severe adverse events [insert used scale] <study XXX> Grade ≥ 3 Grade 3 Grade 4 Grade 5 <study XXX> Grade ≥ 3 Grade 3 Grade 4 Grade 5 Total[a] Grade ≥ 3 (p_H = <XXX>; I^2 = <YYY>) Grade ≥ 3						
Treatment discontinuation due to adverse events <study XXX> <study XXX> Total[a] (p_H = <XXX>; I^2 = <YYY>)						
Treatment interruption due to adverse events <study XXX> <study XXX> Total[a] (p_H = <XXX>; I^2 = <YYY>)						
Suspected unexpected serious adverse reaction <study XXX>						

Time point Outcome Study reference/ID	<Intervention> N	<Intervention> Patients with event n (%)	<Comparator> N	<Comparator> Patients with event n (%)	<Intervention> vs. <Comparator> RR [95 % -CI]	<Intervention> vs. <Comparator> RD [95 % -CI]
<study XXX>						
Total[a] (p_H = <XXX>; I^2 = <YYY>)						
Specific adverse event A[b]						
<study XXX>						
<study XXX>						
Total[a] (p_H = <XXX>; I^2 = <YYY>)						
Specific adverse event B[b]						
<study XXX>						
<study XXX>						
Total[a] (p_H = <XXX>; I^2 = <YYY>)						
a: calculated from meta-analysis b: As requested by member state(s) in their PICOs						
AE: adverse event; N: number of randomized patients; n: number of patients with event; PICO: Population – Intervention – Comparator – Outcome; SAE: serious adverse event						

C.3.2 Safety outcomes – disaggregated, by SOC and PT

If the full list of adverse events appears too long, assessors can decide to apply appropriated cut-off values (e.g. adverse events that occurred in at least one study arm in ≥ 5 % of the patients [depending on the study size]). In this case, please refer to the full data set that will be provided in the submission dossier.

Table 26: Adverse events (all) by SOC and PT

Time point **Study reference/ID** **Safety outcome** SOC PT	**<Intervention>** **N=** **Patients with event n (%)**	**<Comparator>** **N=** **Patients with event n (%)**	**<Intervention> vs. <comparator>** **RR [95 %-CI]; p-value**	**<Intervention> vs. <comparator>** **RD [95 %-CI]; p-value**
<time point>				
Total AE				
System organ class A				
AE1				
AE2				
System organ class B				
AE1				
AE2				
System organ class C				
AE1				
AE2				

footnotes (this line can be deleted if it is not needed)

AE: adverse event, CI: Confidence interval; N: number of randomized patients; n: number of patients with event; PT: Preferred Term, RD: relative difference , RR: relative risk, SOC: System Organ Class

Table 27: Adverse events (serious) by SOC and PT

Time point **Study reference/ID** **Safety outcome** SOC PT	**<Intervention>** **N=** **Patients with event n (%)**	**<Comparator>** **N=** **Patients with event n (%)**	**<Intervention> vs. <comparator>** **RR [95 %-CI]; p-value**	**<Intervention> vs. <comparator>** **RD [95 %-CI]; p-value**
<time point>				
Total SAE				
System organ class A				
SAE1				
SAE2				
System organ class B				
SAE1				
SAE2				
System organ class C				
SAE1				
SAE2				

footnotes (this line can be deleted if it is not needed)

CI: Confidence interval; N: number of randomized patients; n: number of patients with event; PT: preferred Term, RD: relative difference , RR: relative risk, SAE: serious adverse event, SOC: System Organ Class

Table 28: Discontinuation due to adverse events by SOC and PT

Time point **Study reference/ID** **Safety outcome** SOC PT	**<Intervention>** **N=** **Patients with event n (%)**	**<Comparator>** **N=** **Patients with event n (%)**	**<Intervention> vs. <comparator>** **RR [95 %-CI]; p-value**	**<Intervention> vs. <comparator>** **RD [95 %-CI]; p-value**
<time point>				
Total discontinuation due to AE				
System organ class A				
AE1				
AE2				
System organ class B				
AE1				
AE2				
System organ class C				
AE1				
AE2				
footnotes (this line can be deleted if it is not needed) AE: adverse event, CI: Confidence interval; N: number of randomized patients; n: number of patients with event; PT: Preferred Term, RD: relative difference , RR: relative risk, SOC: System Organ Class				

Appendix D Partial use of GRADE

To fill in the following table, the information on uncertainties of the evidence from the appropriate tables for each PICO question should be used. For further instructions on categorizing the factors that may affect certainty of evidence please refer to the EUnetHTA framework paper on partial use of GRADE.

Table 29: Uncertainties of the evidence categorized according to the partial use of GRADE for <PICO 1>

Outcome	Design	Factors that may affect certainty of evidence					Number of patients		Effect estimate p-value[a]
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other	Intervention A	Intervention B	
<outcome 1>	<design, number of studies>								
<outcome 2>	<design, number of studies>								

a: Use of an * indicates statistical significance versus a pre-specified alpha-level, use of a # indicates a pre-specified analysis according to the SAP (for individual studies) or evidence synthesis protocol, use of a $ indicates control for multiplicity. Alternatively indicate if no formal hypothesis testing was carried out

abbreviations (this line can be deleted if it is not needed)