HTA CG | MEMBER STATE COORDINATION GROUP ON HEALTH TECHNOLOGY ASSESSMENT

Guidance on filling in the joint clinical assessment (JCA) dossier template – Medicinal products

V1.0

8 October 2024

Adopted on 28 November 2024 by the HTA CG pursuant to Article 3(7), point (d), of Regulation (EU) 2021/2282 on Health Technology Assessment

This document provides guidance on how to fill in the template for the dossier of the joint clinical assessment of a medicinal product set out in Annex I to the Commission Implementing Regulation (EU) 2024/1381 of 23 May 2024. It complements other guidance adopted by the HTA Coordination Group (HTACG) under Article 3(7), point (d) which should also be taken into account, where applicable, when developing the dossier. This guidance is supplemented by a table template collection to provide further details and to support data presentation.

Throughout the document the text of the template set out in Annex I of the Implementing Regulation is presented in grey boxes. For technical reasons section headings cannot be presented in grey boxes. However, the majority of headings are also from the template set out in Annex I. Further guidance on filling in the template is included in plain text.

The provision of information, data, analysis and other evidence in the dossier shall follow international standards of evidence-based medicine and take into account, if available, the methodological guidance adopted by the HTACG under Article 3(7), point (d), of the HTAR where applicable. Any deviations shall be described and justified. The information requested in the dossier template shall be provided in a clear format, preferably in tabular format when possible.

Revision history

Unnecessary lines shall be deleted.

Version	Document	Legal reference	Submission date	Commission's check date
V0.1	Initial dossier	Article 10(2) HTAR		
V0.2	(Updated dossier following Commission's second request)	Article 10(5) HTAR		
V0.3	(Updated dossier following assessors' request for further specifications, clarifications or additional information)	Article 11(2) HTAR		N/A

Version	Document	Legal reference	Submission date	Commission's check date
V0.4	(Updated dossier following changes to the therapeutic indication(s))	Article 16(4) IR		N/A
V0.5	(Updated dossier following re-initiation of a JCA)	Article 10(8) HTAR		N/A
V0.6	(Dossier with the HTD's indications and justification of confidential information)	Article 11(5) HTAR		N/A
etc.				
V1.0	Dossier for publication (without confidential information)	Article 20 IR	N/A	
V1.0.1	(Updated dossier where the JCA report specifies the need for an update and additional evidence for further assessment becomes available)	Article 18(1) IR		N/A
V1.0.2	(Updated dossier provided on the initiative of the HTD where additional evidence for further assessment becomes available)	Article 18(2) IR		N/A
V1.0.3	(Updated dossier following the initiation of an update of a JCA – update of the assessment scope not needed)	Article 18(5) IR		N/A

Version	Document	Legal reference	Submission date	Commission's check date
V1.0.4	(Updated dossier following the initiation of an update of a JCA – update of the assessment scope needed)	Article 18(6) IR		
V1.0.5	(Updated dossier following the initiation of an update of a JCA with the HTD's indications and justification of confidential information)	Article 11(5) HTAR		N/A
etc.				
V2.0	(Dossier for publication following the finalisation of an update of a JCA (without confidential information))	Article 20 IR	N/A	

List of abbreviations

The following list presents suggestions for abbreviations. It can be adapted to the dossier.

Abbreviation	Definition
ATC	Anatomical Therapeutic Chemical
ATMP	Advanced Therapy Medicinal Product
CHMP	Committee for Medicinal Products for Human Use
CSR	Clinical Study Report
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
HTA	Health Technology Assessment
HTACG	Member State Coordination Group on Health Technology Assessment
HTAR	Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU (OJ L 458, 22.12.2021, p. 1, ELI: http://data.europa.eu/eli/reg/2021/2282/oj)
HTD	Health Technology Developer
IR	Commission Implementing Regulation (EU) 2024/1381 of 23 May 2024 laying down, pursuant to Regulation (EU) 2021/2282 on health technology assessment, procedural rules for the interaction during, exchange of information on, and participation in, the preparation and update of JCA of medicinal products for human use at Union level, as well as templates for those joint clinical assessments
JCA	Joint Clinical Assessment
JSC	Joint Scientific Consultation
PICO	A set of parameters for the JCA comprising of: Patient Population – Intervention(s) – Comparator(s) – Health Outcomes
PRIME	Priority Medicines scheme by the European Medicines Agency
PT	Preferred Term
RCT	Randomised Controlled Trial
RoB	Risk of Bias
SmPC	Summary of Product Characteristics
SOC	System Organ Class

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List of Tables

A list of tables should be provided.

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1 Overview

1.1 Information about the medicinal product under assessment and the HTD

This section shall provide:
– the name of the medicinal product under assessment ('the medicinal product'),
– the corporate name and permanent address of the HTD. In case the HTD responsible for the submission of the medicinal product for regulatory approval is different from the HTD submitting the dossier for JCA of the medicinal product, the corporate name and address of both HTDs shall be specified.

<content provided by the HTD>

1.2 Previous assessments under the HTAR

This section shall indicate whether the medicinal product has been subject to an assessment under the HTAR. If the answer is positive, the section shall provide the therapeutic indication, the date and the reference of the previous JCA report.

<content provided by the HTD>

1.3 Executive summary

This section shall provide a concise executive summary of the dossier focusing on the assessment scope as set out pursuant to Article 8(6) of the HTAR and shared with the HTD in the Commission's first request referred to in Article 10(1) of the HTAR ('the assessment scope'). The executive summary shall include:
– the assessment scope, clearly identifying any PICO(s), for which results were not submitted and explaining reasons for their omission,
– a summary of the results on relative effectiveness and relative safety of the medicinal product (e.g. effect measures with statistical precision for each outcome) with regard to the assessment scope, indicating whether the results were based on direct or indirect evidence. The results shall be provided for each PICO separately,
– the degree of certainty of the relative effectiveness and relative safety with regard to the PICO(s).

<content provided by the HTD>

2 Background

2.1 Characterisation of the medical condition to be treated, prevented or diagnosed

2.1.1 Overview of the medical condition

This section shall:
– describe the medical condition, which the medicinal product intends to treat, prevent or diagnose, including criteria for its diagnosis, if available, using a standardised code such as the International Statistical Classification of Diseases and Related Health Problems ('ICD') code or the Diagnostic and Statistical Manual of Mental Disorders ('DSM') code and the version of the code,
– where relevant, describe the main stages and/or subtypes of the medical condition,
– include any prognostic factors that may affect the course of the disease or medical condition and the prognosis of the medical condition without the new treatment,
– present an estimate of the most recent prevalence and/or incidence for the medical condition in the EEA States in which the HTAR applies and, where relevant, describe any profound differences between these EEA States,
– describe the symptoms and burden of the medical condition for patients, including aspects such as pain, disability, psychosocial issues, and other determinants of morbidity and quality of life from a patient perspective,
– for medical conditions that result in disability and/or a need for a family caregiver, and for treatments that result in major organisational changes to the healthcare system (e.g. due to manufacturing constraints) or major associated procedures: briefly describe the organisational and societal impact of the medical condition and its treatment, giving some context for interpretation of outcomes.

References for the statements shall be provided. Full texts of references shall be provided in Appendix D.1.

<content provided by the HTD>

2.1.2 Characterisation of the target patient population

In case the target population is more specific than the overall medical condition, this section shall:
– name and describe the default target patient population(s), i.e. the therapeutic indication proposed by the HTD in the application for marketing authorisation or variation to an existing marketing authorisation submitted to the EMA or where applicable, the therapeutic indication wording from the CHMP positive opinion or from the SmPC,
– describe and justify the proposed position of the target patient population(s) in the patient pathway of care,
– where relevant, take into account sex, age and other specific characteristics,
– describe any patient sub-populations, including the criteria for their identification, if specifically defined in the assessment scope, and further patient sub-populations, if appropriate,
– describe the natural progression of the medical condition (by patient sub-population, if appropriate).

References for the statements shall be provided. Full texts of references shall be provided in Appendix D.1.

<content provided by the HTD>

2.1.3 Clinical management of the medical condition

This section shall:
– describe the care pathway for the medical condition, which the medicinal product intends to treat, prevent or diagnose where relevant, for different stages and/or subtypes of the disease or medical condition or patient sub-populations, with diagrams of the care pathway(s) that include comparator(s),
– where care pathways vary substantially between the EEA States in which the HTAR is applicable, describe these variations in care,
– include a list of relevant clinical guidelines at the European level, e.g. by European medical associations or societies, if available.

References for the statements shall be provided. Full texts of references shall be provided in Appendix D.1.

<content provided by the HTD>

2.2 Characterisation of the medicinal product

2.2.1 Characteristics of the medicinal product

This section shall describe the characteristics of the medicinal product and, in particular, report the following information:
— proprietary name; active substance(s),
— pharmaceutical formulation(s),
— therapeutic indication,
— mechanism of action,
— therapeutic class,
— ATC code where already assigned,
— method of administration,
— doses and dosing frequency,
— duration of treatment, dose adjustments and combinations with other interventions.

References for the statements shall be provided. Full texts of references shall be provided in Appendix D.1.

<content provided by the HTD>

2.2.2 Requirements/instructions for use

This section shall:
— describe any specifically qualified personnel and equipment required to use the medicinal product, including any specific tests or investigations required. Where such equipment has been fully described in Section 2.2.1, the current section shall refer to the above description and state that there are no additional requirements,
— describe any supplies (except generic supplies) required to use the medicinal product, where applicable.
Where relevant and if appropriate, the characterisation of administration and dosing shall be done by sub-population or patient group.

References for the statements shall be provided. Full texts of references shall be provided in Appendix D.1.

<content provided by the HTD>

2.2.3 Regulatory status of the medicinal product

This section shall:
— provide the regulatory status of the medicinal product in the indication considered for this JCA in the EEA States in which the HTAR is applicable, Australia, Canada, China, Japan, United Kingdom, United States of America and other countries if relevant,
— provide details of the procedural pathway of the medicinal product in the EU, such as orphan designation, conditional marketing authorisation with any specific obligations of the conditional marketing authorisation, ATMP, PRIME or paediatric investigation plan ('PIP'),
— detail ongoing or planned early access/compassionate use programs in the EEA,
— specify other marketing authorisations in the EEA States in which the HTAR is applicable for other indications except the indication considered for this JCA, as well as additional indication(s) already submitted to the EMA and under review.

References for the statements shall be provided. Full texts of references shall be provided in Appendix D.1.

<content provided by the HTD>

2.3 JSC related to the JCA

Where the medicinal product has been subject to a JSC under the HTAR, this section shall explain any deviation from the recommended proposition for evidence generation. The recommendations shall be documented in Appendix D.9.

<content provided by the HTD>

3 Assessment scope

This section shall:
— reproduce the assessment scope in the format shared with the HTD in the Commission's first request referred to in Article 10(1) of the HTAR,
— clearly identify any PICO(s), for which results were not submitted and explain the reasons for their omission.

<content provided by the HTD>

4 Description of methods used in the development of the content of the dossier

This section shall describe the methods used in the development of the content of the dossier, taking into account, if available, the methodological guidance adopted by the HTACG pursuant to Article 3(7), point (d), of the HTAR. Any deviations shall be described and justified.

The methods should be described per PICO with enough detail to allow the assessment of the appropriateness of the methods and of the validity and certainty of the results presented in the dossier. If similar methods are used in different PICOs then this should be clearly stated and methods should only be described once.

4.1 Criteria for selecting studies for JCA

This section shall specify the inclusion and exclusion criteria for studies to be considered for this JCA based on the assessment scope and taking into account, if available, the methodological guidance adopted by the HTACG pursuant to Article 3(7), point (d), of the HTAR. Any deviations shall be described and justified. The specification for inclusion and exclusion criteria shall be provided for each PICO, as appropriate.

For studies to be included in the JCA, sufficient documentation is required to allow for the assessment of the study methods and results. Therefore, studies for which only abstracts are available (e. g. from a conference presentation or poster) should be excluded. This should be considered when defining the inclusion and exclusion criteria for studies.

Inclusion and exclusion criteria for studies for PICO 1

<content provided by the HTD>

Inclusion and exclusion criteria for studies for PICO <x>

<content provided by the HTD>

4.2 Information retrieval and selection of relevant studies

4.2.1 Information retrieval

The HTD shall conduct an information retrieval process with the objective of identifying the evidence to be used for the preparation of the dossier.
The following sources of information shall be systematically considered in the retrieval process:
(1) clinical efficacy and safety studies and where relevant, other applicable studies performed or sponsored by the HTD or by third parties in order to include all up-to-date published and unpublished information (data, analyses and any other evidence) from studies on the medicinal product for which the HTD was a sponsor and corresponding information about studies by third parties, if available;
(2) bibliographic databases. The search shall at least be conducted in the National Library of Medicine's bibliographic database (Medline) and the Cochrane Central Register of Controlled Trials database;
(3) study registries and study results registries (clinical trial databases);
(4) HTA reports on the medicinal product subject to the JCA from EEA States in which the HTAR is applicable and from Australia, Canada, the United Kingdom and the United States of America;
(5) the clinical safety and efficacy data included in the submission file to the EMA;
(6) patient registries.
This section shall:
– provide a list of the sources that were systematically searched for studies that are relevant for the JCA according to the assessment scope and indicate the date of each search. The cut-off date for the searches shall be a maximum of 3 months before the submission of the dossier,
– report whether and when new data with relevance for the assessment scope might become available.
All search strategies shall be fully documented in Appendix D.2.

The assessment scope defines the scope of information retrieval. To meet the requirements of a complete dossier, a systematic search for all available evidence for all PICOs defined in the assessment scope needs to be performed.

4.2.1.1 Studies performed or sponsored by the HTD

In order to comply with the requirements of the HTAR to provide all published and unpublished information from studies on the medicinal product (see Section 4.2.1), a list of all studies and their documentation (see Appendices D.4, D.5 and D.6) should be provided with the dossier.

The approach used to identify studies performed or sponsored of the HTD does not need to be described. The complete listing of all studies that were submitted to the regulatory agency (marketing authorization studies) as well as all studies sponsored by the HTD or in which it financially participates or participated is to be provided in section 5.1.1 (List of studies conducted or sponsored by the HTD or by a third party).

The listing should be restricted to studies involving patients in the therapeutic indication for which the present submission dossier is generated (see Section 5.1.1).

<content provided by the HTD>

4.2.1.2 Bibliographic databases

A search of bibliographic databases should be conducted to identify all relevant studies to be included in the JCA according to the assessment scope. Searches should be performed for studies with the medicinal product under assessment and for studies with comparators (if required for indirect comparisons), as appropriate. To avoid the possibility of bias arising from the selection of studies used to connect the network, these additional studies should be identified via a systematic search of the literature, and all possible connecting studies should be considered for inclusion in the network. Once connections have been established via a path or paths of a given length, it is not generally necessary to search for longer connecting paths.

A list of the bibliographic databases that were searched should be provided and the date of each search should be documented. The search strategies should be adapted to the respective database. If any restrictions were made (e.g., filter for language, year or study type) these should be described and justified.

The search in bibliographic databases at least is to be conducted in MEDLINE (inclusive „in-process & other non-indexed citations") and the „Cochrane Central Registry of Controlled Trials" database (see Section 4.2.1). In addition, a search can be conducted in further databases (e.g., Embase, CINAHL, PsycINFO, etc.).

<content provided by the HTD>

4.2.1.3 Study registries and study results registries (clinical trial databases)

A search in publicly available study registries and study results registries should identify all registered ongoing, completed and discontinued studies conducted by the HTD or third parties

and ensure that all registered information on study methodology and results is incorporated in the dossier.

Searches should be performed for studies with the medicinal product under assessment and for studies with comparators (if required for indirect comparisons), as appropriate.

A list of the study registries/study results registries that were searched should be provided and the date of each search should be documented. The search strategy should be adapted to the requirements of each database and its interface. If any restrictions were applied (e.g., limiting by date) these should be described and justified.

The search should at least be performed in the study registries (or study results registries) ClinicalTrials.gov (www.clinicaltrials.gov), Clinical Trials Information System (CTIS: https://euclinicaltrials.eu/), the EU Clinical Trials Registry (EU-CTR, www.clinicaltrialsregister.eu), and the EMA Clinical Data platform (https://clinicaldata.ema.euorpa.eu). In addition, a search can be conducted in subject-specific study registries (e.g., disease-specific study registries) or study registries of individual pharmaceutical companies.

<content provided by the HTD>

4.2.1.4 HTA reports

HTA reports available on the medicinal product subject to the JCA in the indication under assessment from EEA countries and from Australia, Canada, the United Kingdom and the United States of America should be systematically searched on the websites of the national HTA agencies and in the international HTA database.

A list of the sources that were searched should be provided and the date of each search should be documented. The search strategies should be adapted to each information resource, database, and interface. If any restrictions were made (e.g., filter for language, year or study type) these should be described and justified.

<content provided by the HTD>

4.2.1.5 Submission files to the EMA

The clinical safety and efficacy data included in the regulatory submission file to EMA of the medicinal product under assessment shall be searched to ensure that all available information from these studies that is relevant for the JCA are incorporated in the dossier.

It is not necessary to add a description of how the studies were identified from the EMA submission file.

Based on the submission files to the EMA, the main (pivotal) studies of the development programme of the medicinal product under assessment should be identified. If these studies are not included in the data sets used to characterise relative effectiveness and relative safety according to the assessment scope, methods and results of these studies should be presented in Appendix C.

<content provided by the HTD>

4.2.1.6 Patient registries

The systematic searches undertaken to identify information on and from patient registries should be provided.

<content provided by the HTD>

4.2.2 Selection of relevant studies

This section shall document the approach for the selection of relevant studies from the results of the information retrieval according to inclusion and exclusion criteria defined in Section 4.1. This specification shall be provided for each PICO, as appropriate. If the selection process differs from what is suggested by the methodological guidance adopted by the HTACG pursuant to Article 3(7), point (d), of the HTAR, this shall be described and justified.

Based on the assessment scope and the PICOs within that scope, an information retrieval should be conducted for all available evidence. The selection of studies for the assessment of all PICO questions from the full list of available studies should consider comparator scenarios as shown in the figure below.

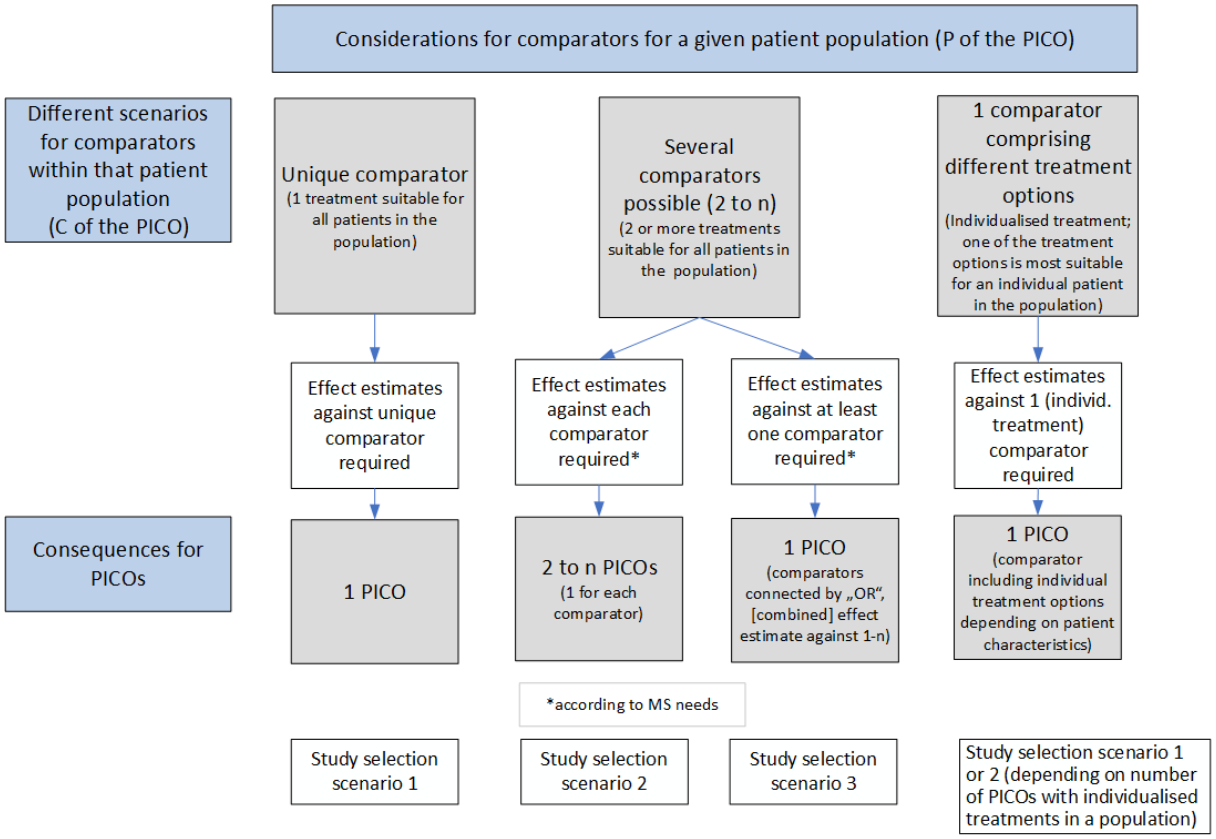

Figure 1: Comparator scenarios and study selection scenarios

Depending on the comparator scenarios included in the assessment scope, the selection of studies from the results of the information retrieval should be carried out as described in the following flowcharts. Study selection and inclusion in the data analysis for the dossier should be concluded as shown in the figures.

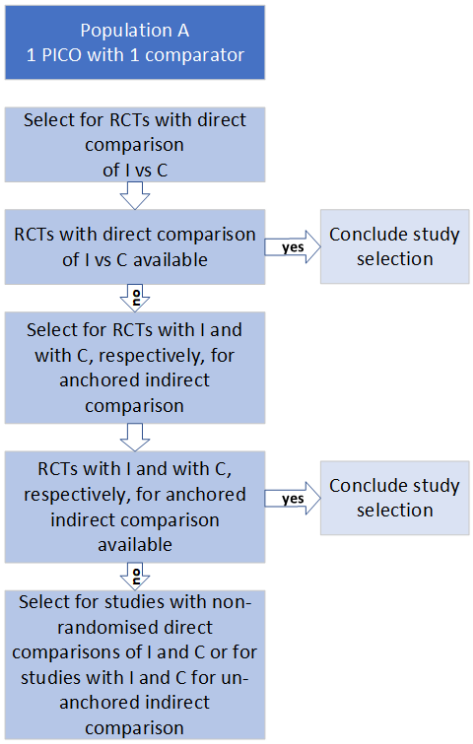

Figure 2: Study selection scenario 1

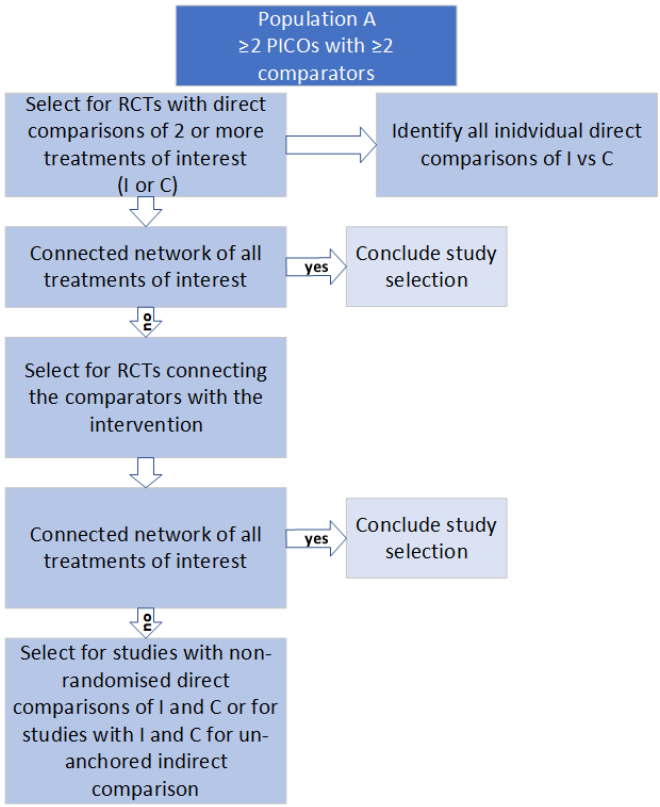

Figure 3: Study selection scenario 2

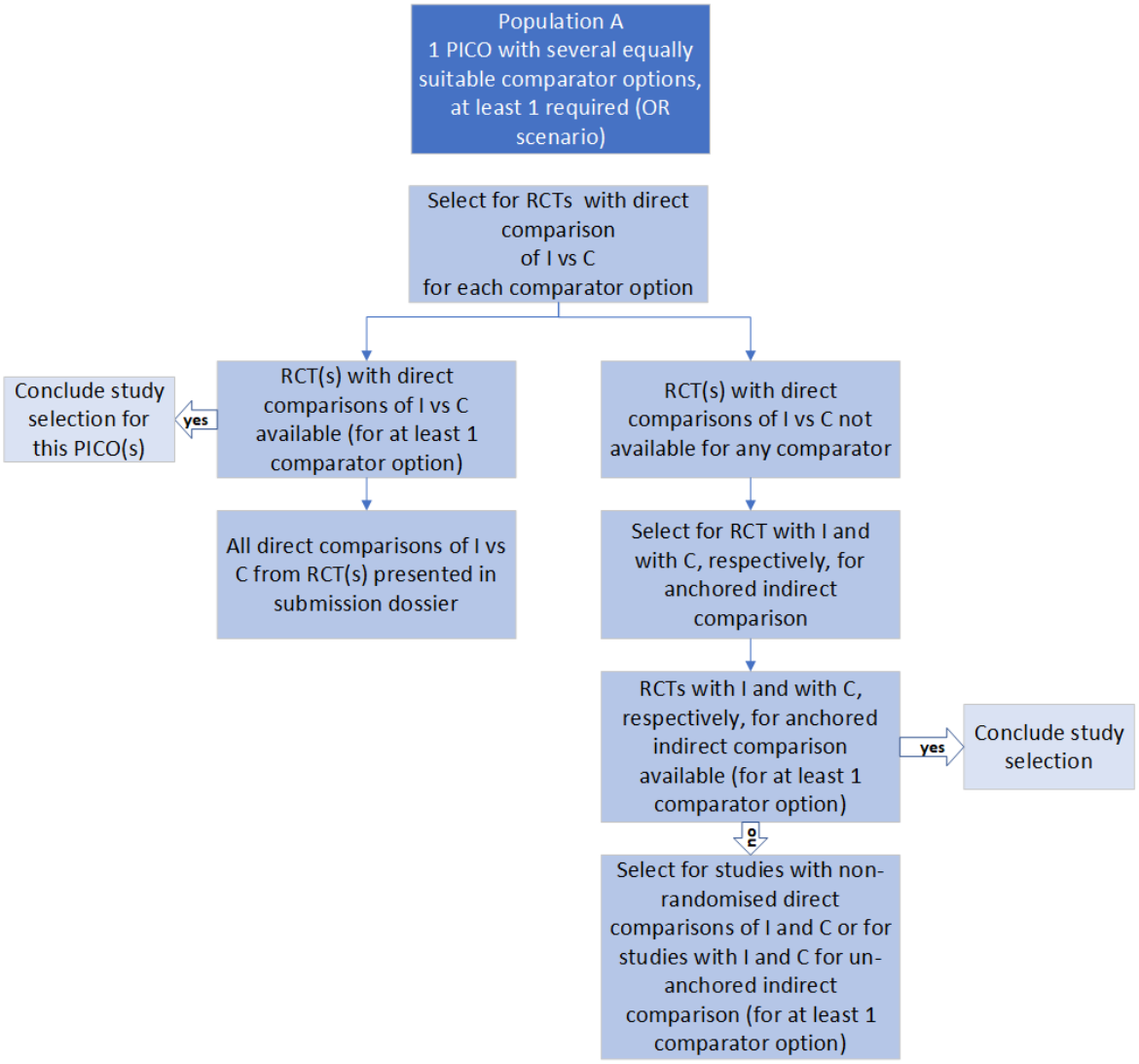

Figure 4: Study selection scenario 2

<content provided by the HTD>

4.3 Data analysis and synthesis

This section shall describe the methods used for data analysis and synthesis. The methods used in the preparation of the dossier and their description shall follow international standards of evidence-based medicine and take into account, if available, the methodological guidance adopted by the HTACG pursuant to Article 3(7), point (d), of the HTAR. Any deviations shall be described and justified.
The underlying documentation for any analysis, i.e. CSR, study protocols and statistical analysis plans (including for evidence syntheses) and details on all software used as well as the respective program code and relevant output shall be provided in the relevant parts of Appendix D.
This section shall cover the following methodological aspects in the following respective sub-sections.

It is a methodological requirement that all results for relative effectiveness and relative safety of the medicinal product are provided for all original clinical studies and for evidence syntheses, respectively. In particular, effect estimates including point estimates, p-values and confidence intervals need to be reported both for individual studies and for evidence syntheses. Also the outcome of the assessment of all model assumptions should be provided.

Any statistical test should be accompanied by the following information:

- prespecified/not prespecified
- appropriately controlled /not appropriately controlled for multiplicity
- significant/not significant against a pre-specified alpha level (if applicable), according to the statistical analysis plan of the corresponding study.
- type of statistical test (e.g. t-test).

If analyses and related calculations other than standard methods (e.g., Mantel-Haenszel) have been used in the development of the dossier, this should be reported and the methods used should be characterised in sufficient detail to allow their assessment.

<content provided by the HTD>

4.3.1 Description of the design and methodology of the included original clinical studies

It is a methodological requirement that the design and methodology of all included original clinical studies are described in the results section of the dossier because this information is needed for the assessment. The information required in the results section includes the

description of methods for estimating effect measures with an evaluation of the plausibility of their underlying assumptions.

The description is to follow reporting standards used in evidence-based medicine (e.g., CONSORT for RCTs, appropriate guidance for other study designs) and take into account the methodological guidance adopted by the HTACG. The reporting standards used for the description of study designs and methods should be described in this section.

<content provided by the HTD>

4.3.2 Description of the results from the original clinical studies

It is a methodological requirement that the results from original clinical studies be presented separately in the results sections of the dossier (section 5), irrespective of any potential synthesis of these results (e.g., in meta-analyses).

This section should describe the items to be presented for the patient characteristics and outcomes. It should include the description of all available operationalisations of the outcomes requested in the assessment scope from each study as well as a justification for the operationalisations presented in the results section.

If outcome measurement instruments such as Patient-Reported Outcome Measures or Clinician Reported Outcome Measures are used for outcome assessment, a table describing their characteristics should be provided (purpose and structure of the instrument, characteristics of the scale(s), boundaries, unit of measurement if any, direction of interpretation). References to the studies assessing the measurement properties (and describing the measurement model, if applicable) of such outcome measurement instruments should be provided. If a responder definition (such as a Minimal Important Difference) was used to interpret the results, its definition and method of definition should be described and justified (with appropriate references to the literature justifying the use of such a responder definition). For each outcome it should be clarified, if the outcome and the specific analyses were pre-specified or not. Any deviations from pre-specification should be described and justified.

Methods for dealing with missing data should be fully described (with specification and justification of the assumed mechanism of generation; e.g., missing completely at random, missing not at random).

<content provided by the HTD>

4.3.3 Direct comparisons by pairwise meta-analyses

The protocol for evidence syntheses, including the relevant statistical analysis plan, shall be provided in Appendix D.5.

It is a methodological requirement that if studies are sufficiently similar (regarding e.g. patients or study design), they should be synthesised quantitatively using meta-analyses. Reporting requirements for meta-analysis include that for each outcome appropriate forest-plots are provided including metrics to estimate the heterogeneity between the included studies (effect estimates including point estimates, confidence intervals and p-values for all studies and the overall effect, the results of the Q-test and I2).

All information in this section should be assigned to the appropriate PICO question(s), if applicable. A detailed description of pairwise meta-analysis methods used, together with justification for their use, should be presented in Appendix B.2 and should follow the requirements outlined therein.

This section shall briefly those methods and their justification. The description shall include:

- the methods used to assess the validity of pooling certain studies and/or excluding others
- the methods used to identify potential treatment effect-modifiers
- the methods used to assess the exchangeability assumptions (i.e., similarity, homogeneity)
- the plausibility of underlying assumptions and methods used to deal with any apparent failure of the exchangeability assumption
- the methods for estimating effect measures
- methods for dealing with missing data

All sensitivity analyses (on methodological parameters) should be listed here (and their respective methods should be briefly described in section 4.3.5, and described in detail in Appendix B.2).

<content provided by the HTD>

4.3.4 Indirect comparisons

The protocol for evidence syntheses, including the relevant statistical analysis plan, shall be provided in Appendix D.5.

In this section the methods used for indirect comparisons and the justification for their use, should be briefly described.

For evidence syntheses involving indirect treatment comparisons, the methods should include:

- an evidence synthesis in the 'population-level' network, including all comparators identified by the assessment scope that form a connected network with the intervention, including results and discussion of heterogeneity and consistency testing, and
- an evidence synthesis in each individual 'comparator-level' network, if these differ from the population-level network, including results and discussion of heterogeneity and consistency testing.

A detailed description of indirect comparison methods used, together with justification for their use, should be presented in Appendix B.2 and should follow the requirements outlined therein. For further details, please refer to the methodological guidance adopted by the HTACG.

This section shall briefly describe indirect comparison methods and provide justification for their use. All information in this section should be assigned to the appropriate PICO question(s), if applicable, i.e. the PICOs for which the specific methods of indirect comparison were used should be identified.

The brief description of indirect comparison methods and justification shall include:

- a description of how the network of evidence was constructed, including selection of connecting paths
- a list of all potentially relevant common comparators and justification for their inclusion/exclusion in the analysis
- the methods used to assess the validity of pooling studies according to the model chosen as well as the exclusion of particular studies from the study pool, if applicable, should be justified
- the graphical illustration of the network of evidence
- the systematic methods used to identify potential treatment effect-modifiers and/or prognostic variables and/or confounders, if applicable
- the methods used to assess the exchangeability assumption
- the plausibility of underlying assumptions and the methods used to deal with any apparent failure of these assumptions (e. g. population-based methods such as matching adjusted indirect comparison
- the methods for estimating effect measures
- methods for dealing with missing data.

It is a methodological requirement that if population-adjusted methods in anchored networks were used, an analysis of baseline characteristics after adjustment (i.e., a description of the population in which the treatment effect has been estimated) and a comparison of results without adjustment is provided. The methods used for these analyses should be briefly described in this section.

All sensitivity analyses conducted (on methodological parameters) should be listed in this section (respective methods shall be briefly described in section 4.3.5, and described in detail in Appendix B.2).

<content provided by the HTD>

4.3.5 Sensitivity analyses

This section shall describe and justify the methods of all performed sensitivity analyses. It shall describe the purpose or which methodological parameter the sensitivity analysis addresses, as well as underlying assumptions.

The methods of all conducted sensitivity analyses shall be briefly described and justified in this section, with a detailed description provided in Appendix B.2.

The results of all sensitivity analyses performed (if needed, to investigate the impact of methodological choices on the robustness of the results) should be described in the results part of the dossier.

<content provided by the HTD>

4.3.6 Subgroup analyses and effect modifiers

Effect modification should be tested with interaction tests and should be investigated via subgroup analyses. This section should report the methods used and list the subgroup analyses which have been conducted. The choice of cut-off values to define subgroups should be justified. It should be described, if the conducted analyses were prespecified in each study and if the analyses were controlled for multiplicity.

<content provided by the HTD>

4.3.7 Specification of further methods as required

This section shall describe any other methods used in deriving results used in the dossier.

<content provided by the HTD>

5 Results

The results presented in the dossier shall follow international standards of evidence-based medicine and take into account, if available, the methodological guidance adopted by the HTACG pursuant to Article 3(7), point (d), of the HTAR. Any deviations shall be described and justified.
The presentation of results shall use text, figures and tables as appropriate.
For relative effectiveness and relative safety, results shall be provided for each clinical study and evidence synthesis, including both direct and indirect comparisons.

5.1 Results from the information retrieval process

Results from the different steps of the information retrieval process shall be presented transparently. For each study, the following information shall be indicated: the study reference ID, the study status, the study duration with data cut-off if applicable, and study arms. For each of the information retrieval steps, the studies not considered in the dossier shall be identified and listed. For each of them, the reason for exclusion shall be specified.
The presentation of the results shall include in the following respective sub-sections:

The latest date of the search(es) should be documented for every search.

5.1.1 List of Studies conducted or sponsored by the HTD or by third parties

This section shall report information on all the studies, conducted or sponsored by the HTD and third parties, referred to in Annex I, point (b), of the HTAR, including all studies providing clinical safety and efficacy data from the submission file to the EMA. The listing shall be restricted to studies involving patients in the therapeutic indication for which the dossier is prepared. The section shall also report whether and when new data with relevance for the assessment scope might become available during the assessment period.

The data presentation in this section, preferably in a tabular format, should include:

- a list of studies performed or sponsored by the HTD in the therapeutic indication for which the dossier is prepared (providing information on the study status, study duration, data cut-off and study arms)
- a list of studies performed or sponsored by the HTD in the therapeutic indication for which the dossier is prepared which are not included in the JCA with reasons for study exclusion

a list of new studies potentially becoming available during the assessment period

The table template collection supplementing this guidance includes empty tables supporting the data presentation (please see tables templates with corresponding table titles). At minimum the information requested in these table templates should be provided.

Corresponding information on studies by third parties, if available, should also be provided.

<content provided by the HTD>

5.1.2 Studies from bibliographic databases

This section shall present results from searches for studies on the medicinal product and its comparator(s) where relevant (e.g. for indirect meta-analyses) in bibliographic databases.

The selection process based on searches in bibliographic databases should be illustrated using a flow-chart including information on the total number of records identified, the number of records after duplicates were removed, the number of records screened by title and abstract including the number of excluded records at this step, the number of full text articles screened as well as the number of records that were excluded after full text screening (including a summary of reasons for exclusion) and the number of resulting relevant records The number of overall studies, to which records contribute, should be stated

The studies not considered in the assessment should be identified. A list of studies excluded during full text review with reasons for exclusion should be provided in Appendix D.2.2.

The data presentation in this section should include:

- an appropriate PRISMA flowchart
- a list of relevant studies identified by the search in bibliographic databases

The table template collection supplementing this guidance includes empty tables supporting the data presentation (please see tables templates with corresponding table titles). At minimum the information requested in these table templates should be provided.

<content provided by the HTD>

5.1.3 Studies from searches in study registries and study result registries (clinical trial databases)

This section shall present results from searches for studies for the medicinal product and its comparator(s) where relevant in study registries/study results registries.

For each relevant (according to the inclusion and exclusion criteria specified for searches in study registries/study result registries) study identified from searches in study registries/study results registries, it should be specified in which registry it was identified, which documentation is available (i.e., study register entry, results reported), if it is included in the list of studies conducted by the HTD and if the study was also identified by searching bibliographic databases. The studies from this list which were not considered in the JCA dossier should be identified. Reasons for exclusion should be specified.

The data presentation in this section should include:

- a list of relevant studies from the searches in study registries
- a list of studies from the searches in study registries not included in the dossier with reasons for study exclusion

The table template collection supplementing this guidance includes empty tables supporting the data presentation (please see tables templates with corresponding table titles). At minimum the information requested in these table templates should be provided.

<content provided by the HTD>

5.1.4 HTA reports

This section shall list HTA reports available on the medicinal product subject to the JCA from EEA States in which the HTAR is applicable and from Australia, Canada, the United Kingdom and the United States of America. The HTA reports shall be provided in Appendix D.7. Any additional relevant evidence identified in those HTA reports which were not identified in other sources shall be listed.

The data presentation in this section should include:

- HTA reports on the medicinal product subject to the JCA in the indication under assessment

The table template collection supplementing this guidance includes empty tables supporting the data presentation (please see tables templates with corresponding table titles). At minimum the information requested in these table templates should be provided.

<content provided by the HTD>

5.1.5 Studies from submission files to the EMA

This section shall list all clinical efficacy and safety studies and where relevant, other applicable studies that were included in the submission file to the EMA. If the main (pivotal) studies were not addressed by any of PICO(s), they shall be presented in Appendix C and be provided in Appendix D.6.

The data presentation in this section should include:

- a list of studies included in the JCA from submission files to EMA including applicable PICO question(s)
- a list of studies not included in the JCA from submission files to EMA including reasons for study exclusion

The table template collection supplementing this guidance includes empty tables supporting the data presentation (please see tables templates with corresponding table titles). At minimum the information requested in these table templates should be provided.

<content provided by the HTD>

5.1.6 Studies from patient registries

This section shall present results from searches for studies for the medicinal product and its comparator(s), where relevant, in patient registries.

References to studies with the medicinal product from patient registries (if available) are to be included in Appendix D.8.

<content provided by the HTD>

5.1.7 List of studies included overall and by PICO question

This section shall define the list of studies included in the description of relative effectiveness and relative safety, informing each PICO.

In this section it should be stated for each (set of) studies informing one or more PICO(s) whether it provides direct or indirect evidence. The comparison under evaluation should be specified. Besides the study reference/ID, the study acronym should be listed as well as the study design and the study intervention and comparator. For each study it should be reported if it was a study for marketing authorization of the medicinal product under assessment, if it was sponsored by the HTD and what kind of documentation is provided within the submission dossier for the JCA.

The tables should include all PICO questions from the assessment scope. If no evidence is provided for a specific PICO question in the assessment scope, this should be recorded under the relevant PICO heading ("No evidence provided by the HTD") and justified. If no evidence is submitted for a PICO question this should be justified.

A tabular listing of all studies included in the description of relative effectiveness and safety shall be provided in Appendix A.

An additional appendix (Appendix C) should also list the main (pivotal) study/studies from the submission file to the EMA, if this/these were not addressed by any of the PICO questions.

The data presentation in this section should include:

- a list of included studies – relevant studies by PICO question

The table template collection supplementing this guidance includes empty tables supporting the data presentation (please see tables templates with corresponding table titles). At minimum the information requested in these table templates should be provided.

<content provided by the HTD>

5.2 Characteristics of included studies

This section shall provide an overview in tabular format of the study design and the study population for all studies included in the description of relative effectiveness and safety in any of PICO(s). Information shall specifically be provided on:
– the study type and design,
– the study date and duration,
– enrolled study population including key eligibility criteria and locations,
– characteristics of the intervention and comparator(s),
– study endpoints,
– if applicable, data cut-off,
– sample size,
– analysis methods.
The study interventions shall be characterised and information on the course of the study (i.e. planned and actual follow-up times per outcome) shall be provided.
The studies included in the dossier shall be described briefly. A detailed description of the study methodology shall be provided in Appendix A.

The data presentation in this section should include:

- the characteristics of the included studies
- the characterisation of the interventions of included studies
- information on the course of included studies – planned follow up times

The table template collection supplementing this guidance includes empty tables supporting the data presentation (please see tables templates with corresponding table titles). At minimum the information requested in these table templates should be provided.

<content provided by the HTD>

5.3 Study results on relative effectiveness and relative safety

This section shall provide results on relative effectiveness and relative safety according to the assessment scope.
This section shall also provide all information that is required to assess the degree of certainty of the relative effects, taking into account the strengths and limitations of the available evidence. The detailed information, which shall include but is not limited to the assessment of the RoB, required to assess the degree of certainty shall take into account, if available, the methodological guidance adopted by the HTACG pursuant to Article 3(7), point (d), of the HTAR. Any deviations shall be described and justified.
Details shall be provided in the relevant Appendixes.

The assessment scope might include one or more PICO question(s). The results on relative effectiveness and relative safety should be presented by PICO question. All PICO questions(s) relevant for a specific patient population should be presented in one chapter. The relative effects versus each relevant comparator should then be presented in sequential sections.

If a study informs more than one PICO, study results may be referenced in the corresponding section by PICO, as appropriate.

<content provided by the HTD>

5.3.1 Results for the patient population <Z-1>

This section shall discuss to which extent the included patient population(s) and/or comparator(s) per study cover the relevant patient population(s)/comparator(s) according to the assessment scope.
Within this section, the results for all PICO(s) addressing patient population <Z-1> shall be presented in sub-sections.
A separate section shall be provided for each patient population <Z-1>, <Z-2>, etc. specified in the PICO(s).
Information shall be provided on the type of the analysed comparison (e.g. direct comparison, adjusted indirect comparison) as well as the relevant study arms per study. If a sub-population of a study was analysed for the assessment, the characteristics of the relevant sub-population shall be described and the number of included patients shall be provided.

The data presentation in this section should include:

- the included studies in the assessment of patient population <Z-1>, <Z-2>, per PICO question

The table template collection supplementing this guidance includes empty tables supporting the data presentation (please see tables templates with corresponding table titles). At minimum the information requested in these table templates should be provided.

Consecutive sections 5.3.2, 5.3.3 etc. should be provided for further, different patient populations. Within each section on a specific patient population, at first the available information should be presented for the specific population (patient characteristics). After that the results on health outcomes should be presented per PICO as outlined below.

<content provided by the HTD>

5.3.1.1 Patient characteristics for <u>population</u> ~~PICO~~ <Z-1>[1]

This section shall present the patient characteristics from all studies covering the relevant patient population included in any of PICO(s). It shall be stated if the included patient populations differ between studies. If only a sub-population of any study represents the relevant population for the JCA, the patient characteristics in this section shall be provided for this appropriate population.

For studies other than RCTs a standardized difference of each patient characteristic between the study arms should be provided. In case of non-randomised comparisons with adjustment for confounding (e.g., based on propensity score matching or weighting) and population-adjusted indirect comparisons, patient characteristics both before and after adjustment should be reported.

The data presentation in this section should include:

- the baseline characteristics as well as treatment/study discontinuations for population <Z-x>
- Subsequent therapy after withdrawal of the study medication; (specifically in oncology studies: information about the first subsequent therapy)

The table template collection supplementing this guidance includes empty tables supporting the data presentation (please see tables templates with corresponding table titles). At minimum the information requested in these table templates should be provided.

<content provided by the HTD>

1 This heading is changed due to an error in Annex I of Commission Implementing Regulation (EU) 2024/1381.

5.3.1.2 Health outcome results for PICO <1> and uncertainties in the results

Within the given patient population, results on health outcomes describing relative effectiveness and relative safety shall be described by PICO in tabular format. The section shall start from describing and justifying the choice of evidence (type of comparison) submitted to address the given PICO <1>.
For any additional PICO question related to a given patient population, a new sub-section presenting the results in terms of health outcomes for this PICO question shall be added.
This section shall provide:
– an overview of the available outcomes (requested in the assessment scope) per study,
– an overview of the course of the included studies, actual treatment duration and observation period for the study intervention and comparator,
– a description of the evidence synthesis method used, including the associated strengths and limitations, together with any factors arising from these methods and their application which may affect the certainty of the evidence,
– the requested results on relative effectiveness and relative safety (i.e. the relative effects of the medicinal product versus the comparator). It shall include the results from all individual studies, as well as the quantitative syntheses of results, e.g. from meta-analyses. The results of the analyses of each of the presented outcomes shall be described briefly. It shall be clarified whether the evidence comes from direct or indirect comparison. If results are reported for data cut-offs, results for all outcomes shall be provided. Reported data cut-offs shall be justified. Information on the amount of missing data and reasons for missing data as well as results for all sensitivity analyses shall be provided,
– a description of any issues affecting the degree of certainty of the relative effects.

Type of comparison

For each PICO the type of comparison should be described including the strengths and weaknesses given the specific available data set.

Available outcomes

An overview of the available outcomes (requested in the assessment scope) per study should be presented using an appropriate table provided in the table template collection. This listing should include all relevant outcomes requested in the assessment scope. It should be specified, if the outcomes were measured in each study.

I If data on an alternative outcome, intended to serve as a surrogate outcome for a specific outcome requested in the scope, are submitted, this should be described. It should be explained for which outcome of interest surrogacy is claimed and the demonstration of the

strength of the association between the surrogate outcome and the outcome of interest and treatments effects should be provided.

To further specify the available data, the treatment duration in the included studies and the observation period for each outcome should be provided.

The data presentation in this section should include:

- the matrix of outcomes in the included studies for PICO <X>
- information on the course of included studies – including actual treatment duration and observation periods

The table template collection supplementing this guidance includes empty tables supporting the data presentation (please see tables templates with corresponding table titles). At minimum the information requested in these table templates should be provided.

Information for risk of bias assessment

No RoB assessment of the original clinical study/studies should be conducted by the HTD itself, but the HTD should provide all relevant information that is required for an appropriate RoB assessment to be performed by the assessment team during the JCA. The HTD should provide the information requested by the signalling questions of the risk of bias tool and reference e.g., sections from the respective clinical study report(s) (if available) or from publications on which the information is based. The following RoB tools should be used:

- RCT: Cochrane RoB 1.0
- non-randomised studies other than uncontrolled trials, cross-sectional studies and case (report) series: Cochrane ROBINS-I

No RoB information is required for uncontrolled trials, cross-sectional studies and case (report) series.

The completed RoB tool signalling questions should be provided in Appendix B.

Results on relative effectiveness and relative safety

The presentation of relative effectiveness and relative safety should include the results from all individual studies as well as any quantitative syntheses of results, for example, from meta-analyses. The results of the analyses of each of the presented outcomes should be described briefly in a text below the tables.

Detailed methodological guidance for the presentation of outcomes in the JCA adopted by the HTACG pursuant to Article 3(7), point (d), of the HTAR and should be taken into account.

The relative effects of the medicinal product versus the comparator should be presented using appropriate tables from the table template collection. The minimum information that should be provided is:

- the operationalization for an outcome for each study (see instructions for outcomes measurement instruments in the methods section),
- results of the intention-to-treat (ITT) analysis (deviations from using the ITT or additional presentation of results from other analysis population(s), if considered appropriate, should be justified),
- number of patients included in the analysis (including information about the extent of missing data and the handling of partially or completely missing data in the analysis),
- results per treatment group (using data types that correspond to the outcome),
- appropriate populational summary measures (position and dispersion) depending on the type of outcome (e.g., number and proportions of events per group for dichotomous outcomes),
- in case of longitudinal observations, populational summary measures (position and dispersion) of the outcome at study start and study end,
- in case of time-to-event data, Kaplan-Meier-curves should be provided including numbers for patients at risk and number of censored patients over the course of the study
- appropriate effect measure, p-value for the corresponding test and appropriate measure of statistical precision
- effect measures for safety outcomes should only be presented in Appendix A2
- statistical method applied (including if applicable: the covariates used for adjustment),
- in case of relevant differences in observation periods between treatment groups: appropriate analysis methods (e.g., survival analysis, including Kaplan-Meier curves) should be conducted for all outcomes (including adverse events (AEs)) for which this would be applicable.

For every outcome it should be reported, if each statistical test conducted was:

- significant against the alpha-level specified in the statistical analysis plan of the corresponding study (significant yes or no or no alpha-level was specified a priori, respectively),
- pre-specified or not according to the statistical analysis plan of the corresponding study,
- appropriately controlled for multiplicity or not.

If results are reported for interim or final data cut-offs, results for all outcomes should be provided, even if the data cut-off was originally planned only for a subset of endpoints. Data cut-offs reported should take into consideration the methodological guidance adopted by the HTACG pursuant to Article 3(7), point (d), of the HTAR.

Only descriptive safety results should be included in this section for the following safety outcomes, if included the assessment scope: AE, serious AE, severe AE, death related to AE, treatment discontinuation due to AE and treatment interruption due to AE. This data presentation should only include absolute numbers of patients with events and percentages per treatment arm without relative effect estimates and nominal p-values. Results for relative safety (i.e. relative effect estimates, nominal p-values and 95% confidence intervals for the AE categories described above and in addition for AEs according to system organ class (SOC) and preferred term (PT) should be provided in a dedicated appendix of the dossier (Appendix A.2). AE according to SOC and PT of any severity should only be included in the appendix if they occur with an incidence of ≥ 5 % in any treatment group. Serious and severe AE (e.g. according to Common Terminology Criteria for Adverse Events Grade ≥ 3) must be included regardless of their incidence.

Evidence synthesis

The methodological and reporting guidance for evidence syntheses are laid down in the methodological guidance adopted by the HTACG pursuant to Article 3(7), point (d), of the HTAR and in the methods section of this guidance. In addition, Appendix B.2 provides detailed requirements for the evaluation of assumptions of the methods used for evidence syntheses. The appendix also describes requirements for information to be provided on the results of evidence syntheses.

The data presentation should include the results from all individual studies as well as any syntheses of results.

Subgroup analysis

In addition to the requirements for reporting of results mentioned above the following aspects should be reported:

- an overview of all subgroup analyses for the relevant outcomes including
  - results (p-values) of the interaction tests for all subgroup analyses conducted,
  - results of all subgroup analyses with a statistically significant interaction test (according to the pre-specified alpha level of the SAP or a nominal p-value < 0.05),
  - in addition, results for subgroup analyses specifically requested in a given PICO should be reported.

The table template collection supplementing this guidance includes empty tables supporting the data presentation (please see tables templates with corresponding table titles). At minimum the information requested in these table templates should be provided.

The results of all subgroup analyses conducted should be provided in appendix A.3.

Sensitivity analyses

Information on the amount of and the reasons for missing data as well as results for all sensitivity analyses conducted should be provided.

Presentation of results on health outcomes

The data presentation in this section should include:

- the relative effectiveness results for <PICO X>
- the descriptive safety results for <PICO X> (with reference to relative safety outcomes and safety outcomes by SOC and PT for <PICO X> in an appendix)
- subgroup analyses for <PICO X>

The table template collection supplementing this guidance includes empty tables supporting the data presentation (please see tables templates with corresponding table titles). At minimum the information requested in these table templates should be provided.

<content provided by the HTD on all aspects described above>

5.3.1.3 Health outcome results for PICO <X> and uncertainties in the results

Results for health outcomes of any additional PICO should be presented as described in the section above.

6 List of references

Appendix A Additional detailed information

A.1 Tables listing and information on methods of all studies included in the JCA

The appendix shall include a line listing of all studies included in the description of relative effectiveness and relative safety. In addition, information on study methods and a patient flow chart shall be provided for each of the listed studies.

The data presentation in this Appendix A.1 should include:

- the included studies in the description of relative effectiveness and relative safety within the assessment scope
- the study design and methodology for study <Study Name>
- a patient flow chart for each study.

The table template collection supplementing this guidance includes empty tables supporting the data presentation (please see tables templates with corresponding table titles). At minimum the information requested in these table templates should be provided.

A.2 Adverse events by System Organ Class and Preferred Term

The data presentation in this Appendix A.2 should include:

- the safety outcomes including effect estimates for <PICO X>
- the safety outcomes by SOC and PT for <PICO X>

The table template collection supplementing this guidance includes empty tables supporting the data presentation (please see tables templates with corresponding table titles). At minimum the information requested in these table templates should be provided.

A.3 Subgroup analyses (if applicable)

A.4 Further analyses (if applicable)

Appendix B Information to assess the degree of certainty of the relative effects (including, but not limited to, the RoB)

B.1 Information for RoB assessment

To enable the assessment of RoB, the signalling questions including the answers should be provided in this appendix.

B.2 Information for the assessment of evidence syntheses

To enable the assessment of the certainty of relative effects from evidence syntheses, a detailed description of the methods and results of evidence syntheses should be provided in this appendix, including the following information and taking account of methodological guidance adopted by the HTACG.

Assessment of assumptions for evidence synthesis

- Details of the process used to identify potential treatment effect-modifiers, which may include
  - Summary of relevant literature
  - Quantitative analysis of subgroup effects and treatment by covariate interaction terms
  - Qualitative assessment of study characteristics and the potential for effect-modification (e.g., inclusion criteria, duration of follow-up, definitions and measurement of outcomes etc.)
  - Transcripts or summaries of clinical opinion received
- Details of the assessment of the exchangeability assumption. This should include assessment of the properties of:
  - Similarity
    - Comparison of the distributions of effect-modifiers across studies (including both patient- and study-level effect-modifiers)
  - Homogeneity
    - Forest plots
    - Results of statistical tests such as Q-test
    - Summary measures such as I^2
  - Consistency (if applicable)
    - Results of Bucher's test for consistency

- For inconsistency models: Deviance and deviance information criterion (DIC) statistics, plots of individual data points' posterior mean deviance for the original model versus the inconsistency model
- For node-splitting methods: Residual deviance, DIC and heterogeneity parameter (if relevant) for the original and split-node network meta-analysis (NMA)

Evidence to support the chosen method of analysis

- Justification for the chosen method/model used for evidence synthesis. Typically, this will make reference to the following:
  - The shape of the network and the number of included studies
  - The availability (or not) of individual patient-level data (IPD)
  - Design features of the included studies relevant for potential heterogeneity
  - The extent of expected and observed heterogeneity (e.g., when choosing a fixed-effect or random-effects model)
  - Any apparent failure of the exchangeability assumption, e.g., to justify the use of meta-regression, restriction to subgroups, or the use of population-adjustment
  - The plausibility of underlying assumptions (e.g., choice between fixed-effect and random-effects model, proportional hazards for survival data)
  - Transcripts or summary of clinical opinion if used to inform the selection of the method
  - Plots assessing visual fit of the model to the extracted data
  - For some methods of evidence synthesis, further model selection work is needed, which may include choosing between different functional forms (e.g., the choice of powers in fractional polynomials) or covariate selection (network meta-regression or population adjustment). In these cases, the model selection procedure must be clearly described, for example with reference to
    - Measures of statistical fit (e.g., Akaike information criterion (AIC), Bayesian information criterion (BIC), DIC)
    - Diagnostic plots
    - Published literature

Additional methods-specific reporting requirements

- For indirect comparisons:

- A listing of all potentially relevant common comparators, justification of choices for inclusion and exclusion of comparators, highlighting any risk of bias arising from the exclusion of comparators from the network
- A listing of all potentially relevant studies for inclusion in the analysis, justification of choices for inclusion and exclusion of studies, highlighting any risk of bias arising from the exclusion of studies in the network
- The shape of the network including a description of how the network of evidence was constructed, how the connecting paths were selected
- Assessment of the extent to which the studies included in the evidence synthesis reflect the specific PICO

- For time-to-event (survival) endpoints, assessment of the proportional hazards assumption, e.g.
  - Diagnostic plots: Log-cumulative hazard plots, Schoenfeld residuals
  - Results of statistical tests for proportional hazards
  - Transcripts or summary of clinical opinion if relevant
  - Full details of the method used for digitisation of published Kaplan-Meier curves (if this has been carried out)
  - If the proportional hazards assumption is rejected and an alternative method is to be used (e.g., fractional polynomials) then the chosen method must be justified
- For Bayesian approaches to pairwise and network meta-analysis:
  - Justification for the applied prior distributions for model parameters
  - Results of sensitivity analysis on prior distributions
- For population-adjusted methods of indirect comparison [matching-adjusted indirect comparison (MAIC), simulated treatment comparison (STC), multilevel network meta-regression (ML-NMR)]:
  - Complete description of model and covariate selection procedure
  - Assessment of covariate overlap and feasibility of population adjustment
  - Analysis of baseline characteristics after adjustment, i.e., a description of the population in which the treatment effect has been estimated
  - Comparison of population-adjusted results with those of ‘standard’ methods (i.e., without population adjustment)
- For evidence synthesis in disconnected networks:

- A complete list of the potential prognostic variables identified, as well as a full description of the methodology used to identify them; this may include for example
  - A search of the relevant literature and a summary of the conclusions drawn
  - Analysis of IPD or published summary data from the included studies or other external data (e.g., registries)
  - Summary or transcripts of clinical opinion received
- A comparison of baseline prognostic characteristics across studies
- Analysis of study-level characteristics that could potentially affect absolute outcomes

- For matching IPD to single-arm trials or other non-randomised data using propensity score (PS) methods or other methods to adjust for confounding:
  - Complete description of model and covariate selection procedure
  - Study protocol for external control study/full description of eligibility criteria/ participant flow
  - Assessment of positivity assumption, e.g., comparison of study inclusion criteria and baseline characteristics
  - Analysis of baseline characteristics after adjustment, including clear description of the inferential goal and target population
  - Histograms or density plot of PS for assessment of overlap
  - Assessment of balance after matching, e.g., standardised mean differences

Software

- Details on all software used including which version
- Code used for all analyses which cannot be clearly described using an explicit standard method (such as Mantel-Haenszel method for a fixed-effect model in the case of binary data)
- Input data used to conduct the analysis, including a precise description of all input variables and how they were derived (note: the HTD is not required to provide individual patient data, only aggregated data such as effect estimates with standard errors are required).
- Where Markov Chain Monte Carlo (MCMC) methods have been used (typically in Bayesian methods):
  - Number of Markov chains with baseline values
  - Number of iterations for the burn-in period and the update period

- Method for the assessment of the convergence of the Markov chains with results

Reporting of results

- Results:
  - Forest plots for all direct comparisons including the effect estimates, p-values, confidence intervals for all studies and the overall effect, the results of the Q-test, and I^2
  - In the case of random-effects models, the estimated between-study standard deviation and the prediction interval for the treatment effect
  - Graphs such as posterior distributions in a Bayesian analysis
  - Surfaces under the cumulative ranking curve (SUCRAs)
- Results of sensitivity analysis: In many situations, model selection (including covariate selection where relevant) will involve a matter of judgement, and other alternative models may be equally or similarly plausible. More generally, the impact of modelling choices on the results should always be explored. The results of sensitivity analysis on model choice should therefore be reported, and their impact on the results should be discussed. Examples of relevant sensitivity analyses may include:
  - Fitting fixed-effects models where random-effects have been used in the base case and vice-versa
  - Fitting models with alternative covariates (e.g., for population adjustment or propensity-score methods) or different functional forms
  - Alternative prior distributions for Bayesian models
  - Carrying out indirect comparisons both with and without population adjustment

Appendix C Results of the main study/studies from the clinical development programme of the medicinal product under assessment (if not included in the presentation by PICO question(s))

The data presentation in this Appendix C should include:

- the main study/studies from the clinical development programme (if not addressed by any of the PICO questions)
- the study design and methodology for this study/these studies
- the data presentation should include a patient flow chart for each study.

The table template collection supplementing this guidance includes empty tables supporting the data presentation (please see tables templates with corresponding table titles). At minimum the information requested in these table templates should be provided.

If not addressed by any of the PICO question(s) the main study/studies of the clinical development programme of the medicinal product under assessment are listed and described.

The following information on the main study/studies is to be provided in this appendix:

- Characteristics of the main study/main studies
- Patient characteristics
- Outcomes

The table template collection supplementing this guidance includes empty tables supporting the data presentation (please see tables templates with corresponding table titles). At minimum the information requested in these table templates should be provided.

Appendix D Underlying documentation

D.1 Full texts of references

In addition to full texts of all references, a RIS file should be provided for each reference list.

D.2 Documentation of information retrieval

D.2.1 Documentation of search strategies for each information source

D.2.2 Results of the information retrieval in standard format

All search results should be provided as RIS files.

D.3 Programming code for programs used for analyses

This appendix shall provide program code and relevant output if the analyses and corresponding calculations cannot be described by a specific standard method.

D.4 Study reports for original clinical studies

This appendix shall provide CSRs, including study protocols and statistical analysis plans, referred to Annex I, point (b), of the HTAR.

D.5 Study reports for evidence synthesis studies

This appendix shall provide all up-to-date published and unpublished information and data-analyses, including study protocols and statistical analysis plans, referred to in Annex I, point (b), of the HTAR required for evidence synthesis studies.

D.6 Clinical safety and efficacy data included in the submission file to the EMA

This appendix shall provide Modules 2.5, 2.7.3 and 2.7.4 of the CTD (format of submission to the EMA) and CSRs (see Section C.4 Study reports in the CSR). For each study, the CSR shall be provided only once.

D.7 HTA reports of the medicinal product subject to the JCA

D.8 Information on studies based on registries

This appendix shall include studies with the medicinal product from patient registries, if available.

D.9 Information on JSCs

The recommendations provided in any relevant JCSs should be provided.