eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

D5.1 Submission Dossier Template – Medicinal Products

Version 1.0, 31/07/2023

Document history and contributors

Version	Date	Description
0.1	15-05-2023	First draft
0.2	27-06-2023	Second draft
0.3	11-07-2023	Draft for CSCQ validation
0.4	26-07-2023	Endorsed by CEB
1.0	31-07-2023	Date of 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, St James Hospital (NCPE), Ireland
Project Management	Zorginstituut Nederland (ZIN), The Netherlands
CSCQ **CEB**	Agencia Española de Medicamentos y Productos Sanitarios [AEMPS], Spain Austrian Institute for Health Technology Assessment (AIHTA), Austria Belgian Health Care Knowledge Centre (KCE), Belgium Gemeinsamer Bundesausschuss (G-BA), Germany Haute Autorité de Santé (HAS), France Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG), Germany Italian Medicines Agency (AIFA), Italy National Authority of Medicines and Health Products, I.P. (INFARMED), Portugal National Institute of Pharmacy and Nutrition (NIPN), Hungary Norwegian Medicines Agency (NOMA), Norway The Dental and Pharmaceutical Benefits Agency (TLV), Sweden Zorginstituut Nederland (ZIN), The Netherlands

The work in EUnetHTA 21 was 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 HTAb

The draft deliverable was reviewed by associated HTAb. The draft template was not open for public consultation, as the draft guidance on the submission dossier template underwent public consultation between 04.07.2022 and 02.08.2022. Furthermore, a dedicated meeting was held with Health Technology Developers on July 13, 2023 to discuss the template.

Associated HTA bodies who reviewed	Dachverband der Österreichischen Sozialversicherung, [DVSV], Austria Norwegian Institute of Public Health, [NIPH], Norway Evaluation and Planning Unit – Directorate of the Canary Islands Health Service, [SESCS], Spain Regione Emilia-Romagna, [RER], Italy Health Information and Quality Authority [HIQA], Ireland DPA, Malta

Copyright

General requirements for the dossier

According to Regulation (EU) 2021/2282 (Article 9.3) the dossier shall meet the following requirements:

- The evidence submitted is complete with regard to the available studies and data that could inform the assessment.
- The data have been analysed using appropriate methods to answer all the research questions for the assessment.
- The presentation of the data is well structured and transparent, thereby allowing for appropriate assessment within the limited timeframes available.
- The dossier includes the underlying documentation with respect to the information submitted, thereby allowing the assessor and co-assessor to verify the accuracy of that information.

In addition to requirements described in this template, the guidance endorsed by the CEB shall be considered in preparing the HTA submission dossier.

On the structure and content of the submission dossier template

The submission dossier template is based on the submission dossier guidance. The template provides further details concerning the requirements laid down in the guidance and provides a more granular structure for presentation of background information, the methods used to compile the dossier and the results on relative effectiveness and relative safety.

The methods section in the dossier template serves two purposes. Firstly, it provides further guidance on the steps required to develop the dossier content, i.e. the information retrieval and study selection, the presentation of methods and results of original clinical studies and evidence synthesis (if appropriate). Secondly, the methods section provides room to actually describe how a given submission dossier was compiled based on these requirements and how these requirements were fulfilled.

In general, in the submission dossier template requirements are clarified in grey boxes. The content of a given submission dossier can be provided by the HTD below these boxes.

Within the submission dossier table templates are provided up to section 5.1. Table templates for the following sections (Section 5.2 et seq.) are provided in a separate file with table templates (Table Template Collection). This is due to the fact that e.g. tables for patient characteristics or outcomes differ for different data situation (e.g. study design of original study or direct vs. indirect comparison) and including the table templates for these different situations would have made the submission dossier template overly complex. When a submission dossier is prepared, the appropriate table formats can be chosen from the table template collection.

List of abbreviations

The following list presents suggestions for abbreviations. It should be adapted to the dossier. 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
EEA	European Economic Area
EMA	European Medicines Agency
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
JCA	Joint Clinical Assessment
PICO	Population – Intervention – Comparator - Outcome
PT	Preferred Term
RCT	Randomised controlled Trial
SmPC	Summary of Product Characteristics
SOC	System Organ Class

Table of Contents

List of tables

1 Overview

1.1 Administrative information

This section of the dossier shall include information on the HTD responsible for submission of the technology under assessment for regulatory approval as well as on the HTD responsible for the HTA submission dossier.

If the technology under assessment has already been assessed under the HTAR, this shall be described.

Table 1: HTD responsible for the submission of the technology under assessment for regulatory approval

Name of the HTD	
Address	

Table 2: HTD responsible for the HTA submission dossier

Name of the HTD	
Address	

Table 3: Previous assessments of the technology under assessment under the HTAR

Processing number	<XXX> / <not applicable>
Indication	<XXX>
Date of assessment under the HTAR	<XXX> / <not applicable>
Reference of the assessment report	<ref> / <not applicable>

1.2 Executive summary

This section shall provide an executive summary of the content of the dossier focusing on the assessment scope. It shall state the available evidence that was submitted to answer the PICO question(s) of the assessment scope and provide summary results on relative effectiveness (point estimates as well as measure of statistical precision such as confidence intervals for each outcome) as well as on relative safety. It should be clear whether the results of the assessment were based on direct or indirect evidence. Any PICO questions, for which summary results were not submitted, should be clearly identified with reasons for their omission.

Table 4: Assessment scope

Summary of PICO 1

<content by the HTD>

Summary of PICO <x>

<content by the HTD>

2 Background

2.1 Characterisation of the health condition to be treated or diagnosed

2.1.1 Overview of the health condition

In order to provide an overview of the health condition, this section of the dossier shall:

- Describe the disease or health condition in the scope of this joint clinical assessment, including criteria for diagnosis, if available, using a standardised code such as the International Statistical Classification of Diseases and Related Health Problems (ICD) code or Diagnostic and Statistical Manual of Mental Disorders (DSM) code (and the version of the code).
- If relevant, describe the main subtypes and/or stages of the disease or health condition.
- Include any prognostic factors that may affect the course of the disease or health condition and the prognosis of the health condition without the new treatment.
- Present an estimate of the most recent prevalence and/or incidence for the health condition in EEA countries and, if applicable, describe any profound differences between these countries.
- Describe the symptoms and burden of the health condition for patients (including aspects such as pain, disability, psychosocial issues, and other determinants of morbidity and quality of life from a patient perspective).
- Where relevant briefly describe the organisational and societal impact of the health condition and its treatment, giving some context for interpretation of outcomes; this description is specifically relevant for health conditions that result in disability and/or a need for a family caregiver, and for treatments that result in major organisational changes to the health care system, e.g. due to manufacturing constraints (e.g. CAR-T cells) or major associated procedures (e.g. organ transplant).

References for the statements shall be provided.

<content by the HTD>

2.1.2 Characterisation of the target population

In order to characterise the target population(s) for the Joint Clinical Assessment this section of the dossier shall:

- Name and describe the default target population(s) (i.e. the claimed indication submitted by the HTD to the regulatory body or the indication wording from the Committee for

Medicinal Products for Human Use (CHMP) positive opinion or summary of product characteristics (SmPC) for medicinal products.

- Describe and justify the proposed position of the target population(s) in the patient pathway of care.
- If relevant, take into account gender- and age-specific characteristics.
- Describe any subpopulations (including the criteria for identifying them) if specifically defined in the assessment scope and further subpopulations, if appropriate.
- Describe the natural progression of the disease (by subpopulation, if appropriate).

References for the statements shall be provided.

<content by the HTD>

2.1.3 Clinical management of the health condition

In order to characterise the clinical management of the health condition, this section of the dossier shall:

- Describe the clinical pathway of care for the health condition being considered in the joint clinical assessment, as well as, if relevant, for different stages and/or subtypes or subpopulations of the health condition, with diagrams of the care pathway(s) that include alternative interventions.
- If clinical pathways vary substantially between EEA countries, describe these variations in care.
- Include a list of clinical guidelines relevant for the health condition (at the European level).

References for the statements shall be provided.

<content by the HTD>

2.2 Characterisation of the health technology under assessment

2.2.1 Characteristics of the health technology

In this section the characteristics of the technology under assessment as well as information on administration and dosing shall be described.

References for the statements shall be provided.

Table 5: Characteristics of the health technology

Nonproprietary name	
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. In case a final approved version of the SmPC does not yet exist, use the information that was presented at EMA in the regulatory process.>
ATC code	
Drug class	
Drug interactions	
footnotes (please delete this line if it is not needed)	
ATC: Anatomical Therapeutic Chemical; SmPC: Summary of Product Characteristics	

Table 6: Administration and dosing of the health technology

Method of administration	
Doses and dosing frequency	
Duration of treatment (including average length of a course of treatment, anticipated average interval between courses of treatment, anticipated number of repeated courses of treatment, criteria for the ending of treatment, if applicable)	
Information on dose adjustments	
Combination with other interventions	
Information on monitoring required during administration or during the treatment period	
Concomitant treatments required or recommended (such as fluid support, antiemetic agents, antiviral agents or venous thromboembolism prophylaxis)	
footnotes (please delete this line if it is not needed)	
abbreviations (please delete this line if it is not needed)	

Table 7: Contraindications or groups for whom the technology is not recommended

Contraindications	**groups for whom the technology is not recommended**
footnotes (this line can be deleted if it is not needed)	
abbreviations (this line can be deleted if it is not needed)	

2.2.2 Requirements/instructions for use

If applicable, any specifically qualified personnel and the equipment required to use the technology shall be described, including any specific tests or investigations required (e.g., biomarker testing, companion diagnostics, amount and type of biological material needed for IVD). If all such equipment is described in the section above, state here that there are no additional requirements.

If applicable, any supplies (except for generic supplies) required to use the technology shall be described .

References for the statements shall be provided.

<content by the HTD>

2.2.3 Regulatory status of the technology

This section shall describe the regulatory status of the technology under assessment.

Table 8: Regulatory information on the health technology

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 or planned early access/compassionate use programs in the EU	
Pediatric investigation plan (PIP) (yes/no)	
[Other, name if applicable] (yes/no)	
footnotes (this line can be deleted if it is not needed)	
ATMP: Advanced Therapy Medicinal Products; MAH: marketing authorization holder; PRIME: Priority Medicines scheme by EMA; *SmPC: Summary of Product Characteristics*	

Table 9: Marketing authorisations in Europe for other indications not included in the JCA

Indication (verbatim wording)	**Date of approval**	**Organisation issuing approval**
footnotes (this line can be deleted if it is not needed)		
abbreviations (this line can be deleted if it is not needed)		

Table 10: Additional indications already submitted to the EMA

Indication (verbatim wording)	**Date of submission**
footnotes (this line can be deleted if it is not needed)	
abbreviations (this line can be deleted if it is not needed)	

Table 11: Regulatory status in Australia, Canada, China, Japan, the United Kingdom and the United States of America

Country	**Indication (verbatim wording)**	**Regulatory status**
Australia		*<e.g. approved on / submitted on / submission planned>*
Canada		
China		
Japan		
United Kingdom		
United States of America		
footnotes (this line can be deleted if it is not needed)		
abbreviations (this line can be deleted if it is not needed)		

References for the statements shall be provided.

2.3 Joint scientific consultation related to the joint clinical assessment

Any joint scientific consultations for the health technology under assessment at the European level shall be listed. If a health technology has been the subject of a joint scientific consultation by the HTACG, any deviation from the recommended proposition for generation of evidence shall be explained. The recommendations shall be documented in Appendix D.9.

<content by the HTD>

3 Research question and assessment scope

This section shall report the assessment scope of the joint clinical assessment as provided to the HTD.

The assessment scope of the joint clinical assessment as provided by the HTA CG is presented in the following table.

Table 12: Assessment scope of the joint clinical assessment

<include assessment scope as provided by HTACG>

4 Methods used in the development of the dossier content

This section shall include the methods used in the development of the dossier content. The methods shall be described to the level of detail allowing the assessment of their appropriateness and of the validity and certainty of the results presented in the dossier.

The methods shall be based on the international standards of evidence-based medicine. Furthermore, the methods shall follow methodological guidance adopted by the CEB. Any deviations from this guidance shall be described and justified.

The data presented in the dossier shall have been analysed using appropriate methods to answer all research questions of the joint clinical assessment.

4.1 Criteria for selecting studies for joint clinical assessment

Based on the assessment scope and the methodological guidance applicable, inclusion and exclusion criteria for studies to be considered in the joint clinical assessment shall be specified. This specification has to be provided for each PICO question, as appropriate.

Inclusion and exclusion criteria for studies for PICO 1

<content by the HTD>

Inclusion and exclusion criteria for studies for PICO <x>

<content by the HTD>

4.2 Information retrieval and selection of relevant studies

The following sections shall describe by which methods the studies and data available were identified to address each PICO question. These comprehensive methods shall be appropriate to identify all relevant studies systematically.

4.2.1 Systematic information retrieval

4.2.1.1 Studies performed or sponsored by the HTD

To meet the requirements of the HTAR, the dossier shall contain all up-to-date published and unpublished information, data, analyses and other evidence from studies on the health technology for which the HTD was a sponsor. Furthermore, all information available on ongoing or discontinued studies with the health technology for which the HTD is a sponsor or otherwise financially involved has to be made available. Corresponding information on studies by third parties, if available, shall also be provided.

No description of the methodology of information retrieval is required for identification of the studies of the HTD. 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 he financially participates or participated is to be provided in Section 5.1.1 (Studies conducted by the HTD).

The listing should be restricted to studies relevant to the population for which the present submission dossier is generated.

The provided information about the study status for the HTD's list of sponsored studies should not be older than three months at the point in time the dossier is submitted.

4.2.1.2 Bibliographic databases

To identify all relevant studies to be included in the joint clinical assessment according to the assessment scope a search in bibliographic databases shall be conducted.

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

A list of the bibliographic databases that were searched shall be provided and the date of each search shall be documented in this section. The search strategies shall be adapted to the respective database. If any restrictions were made (e.g. filter for language, year or study type) these shall be described and justified. All search strategies, separated by database, shall be fully documented in appendix D.2.

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

The cut-off date for the searches should be a maximum of 3 months before submission of the dossier.

<content 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 shall identify all ongoing, completed and discontinued studies conducted by the HTD or third parties and ensure that all published information on study methodology and results is incorporated in the dossier.

Searches shall be performed for studies with the technology under assessment and for studies with comparators, as appropriate.

A list of the study registries / study results registries that were searched shall be provided and the date of each search shall be documented in this section. The search shall be be conducted individually in each database and using a search strategy adapted for the database in question. If any restrictions were made (e.g. filter year) these shall be described and justified. All search strategies, separated by registry, shall be fully documented in appendix D.2.

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/), EU Clinical Trials Registry (EU-CTR, www.clinicaltrialsregister.eu) and the International Clinical Trials Registry Platform Search Portal (ICTRP Search Portal, the search portal of the WHO). 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.

The cut-off date for the searches should be a maximum of 3 months before submission of the dossier.

<content by the HTD>

4.2.1.4 Submission files to the EMA

The clinical safety and efficacy data included in the submission file of the health technology under assessment to the EMA shall be searched to ensure that all available information on studies that are relevant for the joint clinical assessment are incorporated in the dossier.

No further description of the methodology of information retrieval is required for identification of the studies from the submission file to the EMA.

Based on the submission files to the EMA, the main (pivotal) studies of the development programme of the health technology under assessment shall be identified. If these studies are not included in the presentation on relative effectiveness and relative safety according to the assessment scope, the characteristics and results of these studies shall be presented in Appendix B.

4.2.1.5 HTA reports

This section shall document the systematic searches in appropriate sources to identify information on HTA reports available on the health technology subject to the joint clinical assessment from EEA countries and from Australia, Canada, the United Kingdom and the United States of America.

A list of the sources that were searched shall be provided and the date of each search shall be documented in this section. The search strategies shall be adapted to the respective database. If any restrictions were made (e.g. filter for language, year or study type) these shall be described and justified. All search strategies, separated by database, shall be fully documented in appendix D.2

<content by the HTD>

4.2.2 Selection of relevant studies

Relevant studies to be included in the assessment, specifically for description of the relative effectiveness and relative safety, shall be selected according to inclusion and exclusion criteria defined in section 4.1 for each PICO question.

In this section the approach to select relevant studies from the results of the information retrieval shall be documented. If this process differs from what is suggested by the methodological guidance adopted by the CEB, this shall by justified.

<content by the HTD>

4.3 Data analysis and synthesis

The data presented in the dossier shall have been analysed using appropriate methods. Evaluation of the methods applied by the HTD is part of the joint clinical assessment process. This evaluation addresses the appropriateness of the methods and the validity and certainty of the results on relative effectiveness and relative safety generated using these methods. To allow this assessment, the dossier shall include a transparent description of the methods used when preparing the submission dossier and in the included original clinical studies.

All methods used, the description of these methods, and the justification of appropriateness of these methods shall follow the standards of evidence-based medicine and the guidance adopted by the CEB. Any deviations from the standards shall be described and justified.

For relative effectiveness and relative safety all relevant results should be provided for all original clinical studies and evidence syntheses, especially relevant effect estimates, *p*-values, confidence intervals and the estimated overall effect, and the results of the assessment of all model assumptions. The result of any statistical test must be accompanied by three information: was it prespecified or not, was it appropriately controlled for multiplicity or not, and was it

significant or not against a pre-specified alpha level (if applicable); according to the statistical analysis plan of the corresponding study.

For all analyses, details on all software used including the software version shall be reported. If the analyses and corresponding calculations cannot be described by a specific standard method (e.g., Mantel-Haenszel), this shall be stated. The respective program code and relevant output shall be fully documented in appendix C3.

For details, refer to the guidance adopted by the CEB.

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

The design and methodology of all included original clinical studies shall be described in the dossier. This includes the description of methods for estimating effect measures with the plausibility of their underlying assumptions.

The description shall follow standards of evidence-based medicine (e.g., CONSORT for RCTs, appropriate guidance for other study designs) and the guidance adopted by the CEB. This section shall describe which standards were used for describing the study design and methodology.

<content by the HTD>

4.3.2 Description of the results from the original clinical studies

The results from original clinical studies shall be presented separately in the results sections of the dossier, irrespective of any potential synthesis of these results (e.g., in meta-analyses).

This section shall describe the items to be presented for the patient characteristics and outcomes. It shall 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 shall be provided (purpose and structure of the instrument, characteristics of the scale(s), boundaries, unit of measurement if any, direction of interpretation). References allowing access to the studies assessing the measurement properties (and describing the measurement model) of such outcome measurement instruments shall be made available. If a responder definition (such as a Minimal Important Difference) was used to interpret the results, its definition and method of definition shall be described and justified (with appropriate references to the literature justifying the use of such responder definition).

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 by the HTD>

4.3.3 Direct comparisons by pairwise meta-analyses

If appropriate, the studies available shall be synthesised quantitatively via meta-analyses. All information in this section shall be assigned to the appropriate PICO question(s), if applicable. The protocol for evidence syntheses, including the relevant statistical analysis plan, should be provided as an appendix.

The validity of pooling studies as well as the exclusion of particular studies from the study pool, if applicable, shall be justified. Details on the process used to identify potential treatment effect-modifiers should be described.The methods applied shall be described in this section, the choice of methods shall be justified.This includes methods used to assess the exchangeability assumptions (i.e., similarity, homogeneity), plausibility of underlying assumptions, methods for estimating effect measures, description and methods used to deal with any apparent failure of the exchangeability assumption (e.g., meta-regression, restriction to subgroups), methods for dealing with missing data.

All conducted sensitivity-analyses (on methodological parameters) shall be listed here (respective methods shall be described in section 4.3.5).

<content by the HTD>

4.3.4 Indirect comparisons

In this section the methods used for indirect comparisons shall be described. Indirect comparisons are defined as either evidence synthesis of anchored networks of randomised controlled trial such as network meta-analyses or as external comparisons which are evidence synthesis of unanchored networks of for example two single-arm trials. In general, for the data analysis in unanchored networks, access to individual patient data (IPD) is required. The protocol for evidence syntheses, including the relevant statistical analysis plan, shall be provided as an appendix. For details, refer to the guidance adopted by the CEB.

All information in this section shall be assigned to the appropriate PICO question(s), if applicable.

All potentially relevant common comparators shall be listed and the choice taken shall be justified.

The validity of pooling studies according to the model chosen as well as the exclusion of particular studies from the study pool, if applicable, shall be justified. The network of evidence in the form of a graph shall be provided. Details on the process used to identify potential treatment effect-modifiers and/or prognostic variables and/or confounders, if applicable, shall be reported.

Methods used for assessing the exchangeability assumptions (i.e., for evidence synthesis of anchored networks of randomised controlled trials: similarity, homogeneity, consistency; for external comparisons with full IPD information: positivity, sufficient overlap, sufficient balance (in the case of propensity scores)), assessing the plausibility of underlying assumptions, estimating effect measures, dealing with any apparent failure of the exchangeability assumption (e.g., population adjusted methods such as matching-adjusted indirect comparison), selecting statistical model if applicable (e.g., choice of powers when using fractional polynomials, covariate selection procedure), and dealing with missing data shall be described.

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 shall be provided. If an external comparison with full IPD information has been performed, a clear description of the inferential goal, target population, and analysis of baseline characteristics after adjustment shall be provided.

All conducted sensitivity-analyses (on methodological parameters) shall be listed here (respective methods shall be described in section 4.3.5).

<content by the HTD>

4.3.5 Sensitivity analyses

The methods of all sensitivity analyses performed shall be described and justified. The purpose (which attribute of the estimand (e.g., missing data, intercurrent events) or which methodological parameter (assumption of a statistical model) the sensitivity analysis addresses, as well as underlying assumptions shall be described.

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

<content by the HTD>

4.3.6 Subgroup analyses

Effect modification shall be investigated via subgroup analyses. This section shall report the methods used and the conducted subgroup analyses. The choice of cut-off values shall be justified. It shall be described, if the conducted analyses were prespecified in each study and if it was controlled for multiplicity.

<content by the HTD>

4.3.7 Specification of further methods as required

Any methods used in deriving results in the dossier shall follow the guidance adopted by the CEB, if available.

<content by the HTD>

5 Results

The presentation of results shall use text, figures and tables as appropriate. The results presentation shall consider guidance adopted by the CEB.

5.1 Results from the information retrieval process

5.1.1 Studies performed or sponsored by the HTD

This section shall report all studies on the technology under assessment that were conducted by the HTD. This shall include all studies submitted to the regulatory body for medicinal products (marketing authorisation studies from the clinical safety and efficacy data included in the submission file to the EMA), as well as all studies sponsored by the HTD or in which the HTD was or is financially involved. The listing shall be restricted to studies involving patients in the indication (for medicinal products) for which the submission dossier is prepared. In case that studies from this listing were not included in the assessment this shall be justified. The latest date of the search(es) shall be documented.

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

Table 13: List of studies performed or sponsored by the HTD included in the submission dossier

Study reference / ID	**Study for marketing authorization of the technology under assessment**	**Study status**	**Study duration Data cut-off, if applicable**	**Study arms**
<study A>	*yes / no*	*(completed / determined / ongoing)*	*X months*	*Intervention A, intervention B, placebo*
footnotes (this line can be deleted, if it is not needed)				
abbreviations (this line can be deleted, if it is not needed)				

<content by the HTD>

Table 14: Studies performed or sponsored by the HTD that were not included in the submission dossier

Study reference / ID	**Reasons for study exclusion**
footnotes (this line can be deleted, if it is not needed)	
abbreviations (this line can be deleted, if it is not needed)	

5.1.2 Studies from bibliographic databases

This section shall report the results from searches in bibliographic databases. The selection process shall 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. For the relevant records it shall be stated to how many separate studies they correspond.

The studies not considered in the assessment shall be identified. Reasons for exclusion shall be specified for each study.

The latest date of the search(es) shall be documented.

<PRISMA flow chart to be included>

<content by the HTD>

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

The results from searches in study registries/study results registries shall be presented in this section. For each relevant (according to the inclusion and exclusion criteria specified for searches in study registries / study result registries) study it shall be specified in which registry it was identified, which documentation is available (e.g., 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 joint clinical assessment shall be identified. Reasons for exclusion shall be specified.

The latest date of the search(es) shall be documented.

Table 15: Relevant studies from the search in study registries

Study reference/ID	**Identification locations (Name of the study registry and references[a])**	**Study included in the study list of the HTD (yes/no)**	**Study identified based on search in bibliographic databases (yes/no)**	**Status (completed/ discontinued/ ongoing**
<Study 1>	*NCT 12345 [6, 7]* *EudraCT 1223456 [8, 9]*	*yes*	*no*	*completed*
a: reference of the study registry entry, number (NCT-Number, EudraCT-Number) and, if available, reference of the reports on study design and/or results listed in the study registry				
HTD: health technology developer				

Table 16: Studies from searches in study registries that are not included in the submission dossier

Study reference / ID	**Reasons for study exclusion**
footnotes (this line can be deleted, if it is not needed)	
abbreviations (this line can be deleted, if it is not needed)	

5.1.4 Studies from submission files to the EMA

This section shall list all studies that were included in the submission file to the EMA and specify if the studies were included in the joint clinical assessment. The studies not considered in the joint clinical assessment shall be identified. Reasons for exclusion shall be specified. According to the HTAR the clinical safety and efficacy data included in the submission file tor the EMA shall be provided in the submission dossier for the joint clinical assessment. For details see appendix D.6.

Table 17: Studies from submission files to the EMA

Studies included in the joint clinical assessment	**Applicable PICO question**
<study 1>	PICO <X>
<study 2>	
Studies not included in the joint clinical assessment	**Reasons for study exclusion**
<study 3>	*<specify>*
<study 4>	
footnotes (this line can be deleted, if it is not needed	
abbreviations (this line can be deleted, if it is not needed	

<content by the HTD>

5.1.5 HTA reports

This section shall list HTA reports available on the health technology subject to the joint clinical assessment from EEA countries and from Australia, Canada, the United Kingdom and the United States of America. The HTA reports shall be provided in appendix D.7.

The latest date of the search(es) shall be documented.

Table 18: HTA reports on the health technology subject to the joint clinical assessment

HTA report title	**Country affiliation**
<report 1>	*<specify>*
<report 2>	
footnotes (this line can be deleted, if it is not needed	
abbreviations (this line can be deleted, if it is not needed	

<content by the HTD>

5.1.6 List of studies included overall and by PICO question

This section shall define the list of studies informing each PICO question by using the table below. In this table it shall be stated for each (set of) studies wether it provides direct or indirect evidence. The comparison under evaluation shall be specified. Besides the study reference / ID, the study acronym shall be listed as well as the study design and the study intervention and comparator. For each study it shall be reported if it was a study for marketing authorization of the technology under assessment, if it was sponsored by the HTD and what kind of documentation is provided within the submission dossier for the joint clinical assessment.

The table shall include all PICO questions from the assessment scope. If evidence is not provided for a specific PICO question in the assessment scope, "No evidence provided by the HTD" shall be recorded under the relevant PICO heading. If no evidence is submitted for a PICO question this shall 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 B) shall 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.

Table 19: Included studies – list of relevant studies by PICO question

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 in 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: randomised controlled trial			

<content by the HTD>

5.2 Characteristics of included studies

An overview of the study design and the study population shall be provided for all studies included in the description of relative effectiveness and safety in any of the PICO questions using the tables below. Information shall be provided on the study type and design, on the enrolled study populations (e.g. diagnosis, general severity of disease, line of therapy), the study arms (name of the intervention; dosing, posology etc, shall only be included if necessary to identify the relevant treatment arms for the assessment), study duration including screening, treatment and follow-up as appropriate, data cut-offs (including information on pre-specification or motivation) and study endpoints (primary: primary endpoint of the study; key secondary: only secondary endpoints controlled for multiplicity; other: only if included in the PICO question). The study intervention shall be characterised.

Information on the course of the study, i.e. planned follow-up times per outcome should be provided.

A detailed description of the study methodology shall be provided in Appendix A.

This description shall follow the requirements laid down in guidance adopted by the CEB.

Table 20: Characteristics of the included studies

Table 21: Characterisation of the interventions of included studies

Table 22: Information on the course of included studies – planned follow up times

The studies included in the submission dossier shall be described briefly.

<content by the HTD>

5.3 Study results on relative effectiveness and relative safety

The HTD shall provide aggregated data (results on relative effectiveness and safety) according to the assessment scope in the submission dossier. The analyses presented in the dossier shall take the guidance adopted by the CEB into consideration.

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

5.3.1 Results for the patient population < to be specified>

For each patient population specified in the PICO question(s) according to the assessment scope, a separate section shall be provided. Within this section, the results for all PICO question(s) addressing this patient population shall be presented in subsections.

An overview of the studies included for the assessment of PICO question(s) addressing the patient population shall be provided in the following table. This shall include information 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.

Table 23: Studies included in the assessment of patient population <X> per PICO question

It shall be discussed to which extent the included patient populations and/or comparisons per study cover the relevant population/comparators according to the assessment scope.

<content by the HTD>

5.3.1.1 Patient characteristics

The patient characteristics from all studies covering the relevant patient population included in any of the PICO question(s) addressing this population shall be presented using an appropriate table provided in the table template collection. For studies other than RCTs a standardized difference between the study arms shall be provided. In case of non-randomised comparisons with adjustment for confounding (e.g. based on propensity score matching or weighing) and population-adjusted indirect comparisons, patient characteristics both before and after adjustment shall be reported. If only a sub-population of any study represents the relevant population for the joint clinical assessment, the patient characteristics in this section shall be provided for this appropriate population. The data presentation shall take guidance adopted by the CEB into consideration.

Table 24: Patient baseline characteristics including treatment / study discontinuations for population <x>

The included patient population shall be described in summary. It shall be stated, if the included patient populations differ between studies.

<content by the HTD>

5.3.1.2 Outcomes for PICO <to be specified>

For any PICO question for a given patient population required according to the assessment scope, a new subsection presenting the results for outcomes requested for this PICO question shall be added. The choice of evidence (type of comparison) submitted to address the PICO question shall be described and justified. Methods-specific reporting requirements (e.g. (among others) for population-adjusted methods of indirect comparisons or evidence synthesis in disconnected networks) shall follow the guidance adopted by the CEB.

Type of comparison

<content by the HTD>

Available outcomes

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

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

Table 25: Matrix of outcomes in the included studies for PICO <x-1>

Table 26: Information on the course of included studies – actual treatment duration and observation periods

Information for risk of bias assessment

No risk of bias (RoB) assessment of the original clinical study/studies shall be conducted by the HTD itself, but the HTD shall provide all relevant information that is required for an appropriate RoB assessment to be performed by the assessment team during the joint clinical assessment. For that the HTD shall 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 shall be used:

- RCT: Cochrane RoB 2.0 [reference]
- non-randomised studies other than uncontrolled trials, cross-sectional studies and case (report) series: Cochrane ROBINS-I [reference]

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

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

Results on relative effectiveness and relative safety

The presentation of relative effectiveness and relative safety shall 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 shall be described briefly in a text below the tabular presentation.

Detailed requirements for the presentation of outcomes in the joint clinical assessment are laid down in the guidance adopted by the CEB and shall be followed.

The relative effects of the health technology versus the comparator shall be presented using appropriate tables from the table template collection. Among others the following aspects shall be reported:

- The operationalization for an outcome for each study (see instructions for outcomes measurement instruments, section 4.3.2),
- Results of the ITT analysis (deviations shall 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 dispesion) 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 ,
- Kaplan-Meier-curves shall be provided including numbers for patients at risk in the course of the study
- Appropriate effect measure, p-value for the corresponding test and appropriate measure of statistical precision
- Statistical method applied (incl. If applicable: 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) shall be conducted for all outcomes (including AEs) for which this would be applicable.

For safety outcomes for the following classes of adverse events the frequency of occurrence, the total number of adverse events, absolute and relative risk effect estimates including p-values and the corresponding 95% CI shall be reported:

- all adverse events,
- serious adverse events,
- severe adverse events (grade ≥ 3, grade 3, grade 4, grade 5),
- treatment discontinuation due to adverse events,
- treatment interruption due to adverse events,
- suspected unexpected serious adverse reaction,
- specific adverse events as requested in the assessment scope.

In addition adverse events disaggregated by system organ class (SOC) and preferred term (PT) (MedDRA), for adverse events, serious adverse events and discontinuation due to adverse events shall be provided.

For every outcome it shall 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 data cut-offs, results for all outcomes shall be provided, even if the data cut-off was originally planned only for a subset of endpoints. Data cut-offs reported should be justified.

Evidence synthesis

The reporting requirements for the results of evidence synthesis are laid down in the guidance adopted by the CEB. The data presentation shall include the results from all individual studies as well as any syntheses of results.

If evidence synthesis is conducted, it shall be reported if and how all assumptions of the chosen method are justified. The respective networks shall be illustrated graphically.

Multiple studies shall be combined in a meta-analysis, if the studies are suffiently similar (regarding e.g. patients or study design). For meta-analysis, appropriate forest-plots shall be provided including metrics to estimate the heterogeneity between the included studies (effect estimates, p-values, confidence interval for all studies and the overall effect, the results of the Q-test and $I^{2)}$.

For indirect treatment comparisons the results shall be structured by the following aspects:

- Homogeneity of results: the results for pairwise meta-analysis shall be presented, the amount of heterogeneity shall be discussed.
- The pooled effects shall be presented
- The results for the heterogeneity testing shall be discussed

Subgroup analysis

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

- An overview of all conducted subgroup analyses for the relevant outcomes including information, if they were pre-specified according to a study protocol
- Results (p-values) of the interaction tests for all subgroup analyses conducted
- Results of all subgroup analyses conducted

Missing data

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

<content by the HTD>

Table 27: Relative effectiveness results for PICO <x-1>

Table 28: Relative safety outcomes for PICO <x-1>

Table 29: Safety outcomes by SOC and PT for PICO <x-1>

Table 30: Subgroup analyses for PICO <x-1>

5.3.1.3 Outcomes for PICO <to be specified>

For each PICO question defined for the patient population covered in this section outcomes should be provided as required in section 5.3.1.2.

5.3.2 Results for patient population <to be specified>

For each patient population included in the assessment scope a separate section presenting data according to the requirements of section 5.3.1 including its subsections shall be provided.

6 List of references

Appendix A Tabular listing and information on methods of all studies included in the joint clinical assessment

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

Table 31: Studies included in the description of relative effectiveness and relative safety within the assessment scope

Study reference/ID	**Treatment arm(s) (relevant for the assessment)**	**Study design**
Studies on the technology under assessment		
RCTs		
<study A>	*<intervention> vs. <comparator>*	*RCT*
…		
Non-RCTs		
<study B>	*<intervention> vs. <comparator>*	*<e.g. non-randomised, controlled / single-arm>*
…		
…		
Additional studies on comparators (if required)		
RCTs		
<study C>		RCT
…		
Non-RCTs		
<study D>	*<intervention> vs. <comparator>*	*<e.g. non-randomised, controlled / single-arm>*
…		
footnotes (this line can be deleted if it is not needed)		
abbreviations (this line can be deleted if it is not needed)		

For the presentation of the methodology of each included study the following table template shall be used. For study designs other than RCT appropriate guidance shall be followed. The data sources used to fill in the tables shall be referenced. For each study, a separate version of the table below, including a flow chart for the patient flow shall be generated.

Table 32: Study design and methodology for study <Study Name>

CONSORT Item	**Characteristic**	**Study information**
-	Study objective	
2 b	Precise objectives, problem and hypotheses	
-	Methods	
3	Study design	
3a	Description of the study design (e.g. parallel, factorial) including allocation ratio	

3b	Relevant changes in the methodology after the study has started (e.g. inclusion/ exclusion criteria, with justification	
4	Test subjects / patients	
4a	Inclusion/exclusion criteria for test subjects/patients	
4b	Study organization and location where the study is conducted	
5	Interventions Precise information on the planned interventions in each group and on the administration, etc.	
6	Target criteria	
6a	Clearly defined primary and secondary target criteria, survey times, possibly all survey methods used to optimize the quality of results (e.g. multiple observations, training of the examiners) and possibly information regarding the validation of survey instruments	
6b	Changes in the target criteria after the study has started, with justification	
7	Case number	
7a	How were the case numbers determined?	
7b	If necessary, description of interim analyses and criteria for premature discontinuation of the study	
8	Randomization, generation of treatment sequence	
8a	Method for generating random allocation	
8b	Details (e.g. block randomization, stratification)	
9	Randomization, allocation concealment, execution of allocation (e.g. numbered containers; central randomization by fax/ phone), information if concealment was ensured until allocation	
10	Randomization, execution Who conducted the allocation, who entered the test subjects/patients in the study and who allocated the test subjects/patients to the groups?	
11	Blinding	
11a	Were the a) test subjects/patients and/or b) those who conducted the intervention/ treatment, and/or c) those who assessed the target variables blinded or not blinded, how was blinding performed?	
11b	If relevant, description of the similarity of interventions	
12	Statistical methods	
12a	Statistical methods for assessing the primary and secondary target criteria	
12b	Additional analyses, such as subgroup analyses and adjusted analyses	
-	Results	
13	Patient flow (including flow chart for illustration after the table)	

13a	Number of study participants for each of the treatment groups formed through randomization, who a) were randomised, b) actually received the planned treatment/intervention, c) were considered in the analysis of the primary target criterion	
13b	For each group: Description of lost and excluded patients after randomization including justification	
14	Inclusion / recruitment	
14a	More details on the time period the test subjects/patients started the study and on follow-up monitoring	
14b	Information why the study ended or was terminated	
a: according to CONSORT 2010		

16

17 Present the patient flow in a flow chart for each study.

18 *<content by the HTD>*

19

Appendix B Information for RoB assessment

For each original clinical study included in the submission dossier a completed RoB tool (see section 5.3.1.2) answering the signalling questions including references to all presented information shall be provided without performing a final RoB assessment.

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

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

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

Characteristics of the main study/main studies

Patient characteristics

Outcomes

Table 33: Main study/studies from the clinical development programme (if not addressed by any of the PICO questions)

Main study/ies from the clinical development programme (if not addressed by any of the PICO questions)		
Study reference/ID	**Treatment arm(s)**	**Study design**
RCTs		
<study A>	*<intervention> vs. <comparator>*	*RCT*
…		
Non-RCTs		
<study B>	*<intervention> vs. <comparator>*	*<e.g. non-randomised, controlled / single-arm>*
…		
footnotes (this line can be deleted if it is not needed)		
abbreviations (this line can be deleted if it is not needed)		

For the presentation of the methodology of each included study the following table template shall be used. For each study, a separate version of the table below, including a flow chart for the patient flow shall be generated.

Table 34: Study design and methodology for study <Study Name>

CONSORT Item	**Characteristic**	**Study information**
-	Study objective	
2 b	Precise objectives, problem and hypotheses	
-	Methods	
3	Study design	
3a	Description of the study design (e.g. parallel, factorial) including allocation ratio	

3b	Relevant changes in the methodology after the study has started (e.g. inclusion/ exclusion criteria, with justification	
4	Test subjects / patients	
4a	Inclusion/exclusion criteria for test subjects/patients	
4b	Study organization and location where the study is conducted	
5	Interventions Precise information on the planned interventions in each group and on the administration, etc.	
6	Target criteria	
6a	Clearly defined primary and secondary target criteria, survey times, possibly all survey methods used to optimize the quality of results (e.g. multiple observations, training of the examiners) and possibly information regarding the validation of survey instruments	
6b	Changes in the target criteria after the study has started, with justification	
7	Case number	
7a	How were the case numbers determined?	
7b	If necessary, description of interim analyses and criteria for premature discontinuation of the study	
8	Randomization, generation of treatment sequence	
8a	Method for generating random allocation	
8b	Details (e.g. block randomization, stratification)	
9	Randomization, allocation concealment, execution of allocation (e.g. numbered containers; central randomization by fax/ phone), information if concealment was ensured until allocation	
10	Randomization, execution Who conducted the allocation, who entered the test subjects/patients in the study and who allocated the test subjects/patients to the groups?	
11	Blinding	
11a	Were the a) test subjects/patients and/or b) those who conducted the intervention/ treatment, and/or c) those who assessed the target variables blinded or not blinded, how was blinding performed?	
11b	If relevant, description of the similarity of interventions	
12	Statistical methods	
12a	Statistical methods for assessing the primary and secondary target criteria	
12b	Additional analyses, such as subgroup analyses and adjusted analyses	
-	Results	
13	Patient flow (including flow chart for illustration after the table)	

13a	Number of study participants for each of the treatment groups formed through randomization, who a) were randomised, b) actually received the planned treatment/intervention, c) were considered in the analysis of the primary target criterion	
13b	For each group: Description of lost and excluded patients after randomization including justification	
14	Inclusion / recruitment	
14a	More details on the time period the test subjects/patients started the study and on follow-up monitoring	
14b	Information why the study ended or was terminated	
a: according to CONSORT 2010		

Present the patient flow in a flow chart for each study.

<content by the HTD>

Present further (using appropriate templates from the table template collection):

- Characteristics of the main study/main studies (according to section 5.2)
  - Characteristics of the main study/main studies (Table 20),
  - Characterisation of the interventions of main study/main studies (Table 21),
  - Information on the course of main study/main studies - planned follow up times (Table 22),
- Patient characteristics (according to section 5.3.1.1)
  - Patient baseline characteristics including treatment / study discontinuations (Table 24)
- Outcome data (corresponding to section 5.3.1.2)
  - Matrix of outcomes of the main study/main studies (Table 25)
  - Information on the course of main study/main studies – actual treatment duration and observation periods (Table 26)
  - Appropriate tables reflecting the outcome presentation instruction presented in section 5.3.1.2

<content by the HTD>

Appendix D Underlying documentation for medicinal products

D.1 Full texts of references

Full texts of any references provided in the dossier and listed in the respective reference lists shall be provided. The reference list of the submission dossier shall be provided in a standard format that can be read by literature management programs.

D.2 Documentation of information retrieval

The documentation of information retrieval shall be provided in a standard format that can be read by literature management programs.

D.2.1 Documentation of search strategies for each information source

<content by the HTD>

D.2.2 Results of the information retrieval in standard format

<content by the HTD>

D.3 Programming code for programs used for analyses

Program code and relevant output shall be provided if the analyses and corresponding calculations cannot be described by a specific standard method (e.g. Mantel-Haenszel method for a fixed-effect model in the case of binary data).

Input data that is sufficient to replicate the analysis in a suitable format (e.g., CSV) shall be provided.

Where Markov Chain Monte Carlo (MCMC) methods have been used (typically in Bayesian methods) the following should be provided:

- 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

D.4 Study reports for original clinical studies

The Clinical Study Reports (CSR), including study protocols and statistical analysis plans, required by the Regulation and any guidance adopted by the CEB shall be provided as part of the underlying documentation of the dossier. The technical specifications to be followed for submitting the CSRs will be provided by guidance from the CEB.

D.5 Study reports for evidence synthesis studies

All up-to-date published and unpublished information and data-analyses including study protocols and statistical analysis plans for evidence synthesis studies required by the HTAR

and any guidance adopted by the CEB shall be provided as part of the underlying documentation of the dossier.

D.6 Clinical safety and efficacy data included in the submission file to the European Medicines Agency

Clinical safety and efficacy data included in the submission file to the EMA shall be provided as sections 2.5, 2.7.3 and 2.7.4 from the Common Technical Document (CTD, format of submission to EMA) and as CSRs (see section C.4 Study reports; for each study the CSR shall be provided only once).

D.7 HTA reports of the health technology subject to the joint clinical assessment

If HTA reports from earlier joint clinical assessments or from other jurisdictions are available, these shall be included.

D.8 Information on studies based on registries

If any studies with the health technology under assessment from patient registries are available, these shall be included.

D.9 Information on joint scientific consultations

If a health technology has been subject to a joint scientific consultation, the recommendations shall be provided.