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PICO CONCEPT PAPER

PICO Sub Group

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Assessment team

Rapporteur	RER, Italy
Author(s)	IQWiG, Germany ZIN, Netherlands AIHTA, Austria
Reviewer(s)	AETSA, Spain UCSC/Gemelli, Italy ZIN, Netherlands TLV, Sweden HAS, France
Advisory role	NICE, UK RER, Italy AEMPS Spain AQUAS Spain

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LIST OF ABBREVIATIONS

CA	Collaborative Assessments
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EUnetHTA	European Network of Health Technology Assessment
EUnetHTA	European Network for Health Technology Assessment
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
JA	Joint Assessment
JA3	Joint Action 3
OT	Other Technologies
PICO	Population, Intervention, Comparator, Outcome
(p)MAH	(prospective) Market Authorization Holder
PT	Pharmaceutical Technologies
REA	Relative Effectiveness Assessment
SDAT	Submission Dossier and Assessment Report Template sub group
SOP	Standard Operating Procedure
WP	Work package
WP4	Work Package 4

1 BACKGROUND

Within EUnetHTA there is lack of alignment on the concept of a 'PICO' and its role in the assessment. Furthermore, a guidance on how to develop a "European PICO" is missing. At the same time, a clear definition of a research question (or PICO question, see below) is required to guide the development of a joint assessment. A PICO survey has been set up to collect feedback from partners on relevant PICO-questions, however, the process of integrating this feedback remains unclear. This is a challenging situation for the authoring teams, who are asked to define the PICO question(s) for the EUnetHTA Assessments when preparing the project plan.

Therefore, in September 2019, the Executive Board decided to set up a subgroup to define a standardized process for the development of a European PICO question(s) for joint assessments. The objective of this paper is to:

- Conceptualize EUnetHTA's perspective on the role of the PICO question(s) for EUnetHTA Assessments;
- Define a standard process on how to develop the PICO question(s) for these Assessment.

It is not the objective of this paper to provide a methodological guidance on how to develop the PICO question(s). The results of this paper will be taken further in a dedicated Standard Operating Procedure (SOP) to better guide the authoring teams.

2 METHOD

To develop the concept paper, the sub group drew from all experiences regarding the development of PICO questions in past EUnetHTA assessments. In addition, the sub group liaised closely with the other relevant sub group on pharmaceutical submission and assessment report template group (SDAT). The participants from the SDAT sub group were also asked to raise questions and challenges on the PICO development that should be considered in this concept paper. Results from previous PICO surveys of EUnetHTA assessments and feedback on these surveys were also incorporated. Lastly, there was a consultation of the 2nd draft concept report with the reviewers and advisors of this PICO sub group.

3 THE ROLE OF A PICO QUESTION FOR A EUNETHTA ASSESSMENT

Aim 1 of the task group is to conceptualize EUnetHTA's perspective on the role of a PICO for an assessment.

3.1 *The research question of a HTA*

The starting point for an assessment of a medical intervention is the formulation of a defined research question that should be answered by the assessment. In the context of EUnetHTA the research questions to be investigated are based on policy questions from the health care systems in which a HTA report should be used. Given the diversity of health care systems in Europe, it is possible that for a given medical intervention different policy questions are formulated by different partners.

The assessment of an intervention should not be data driven, i.e. the research questions should not be deduced from the available studies (either identified via an own information retrieval by the authoring team or submitted by the MAH). Rather, an appropriate translation of the policy question into a research question should be performed in the planning stage of the assessment. This means that the research question (the PICO question, see below) is pre-specified for a given assessment.

3.2 *The PICO framework*

The PICO framework provides a standard format for the definition of a research question, e.g. for a comparative assessment of the effectiveness and safety of various treatment options.

Within the PICO framework research questions are defined using (at minimum) the following components:

P (population)	the patients or population(s) in which the intervention under assessment should be used
I (intervention)	the therapeutic, diagnostic or preventive intervention under assessment (incl setting)
C (comparator)	the alternative intervention(s) against which the intervention under assessment should be compared
O (outcomes)	the outcomes of interest (if relevant incl. minimum follow-up time)

Because of different policy questions from different partners (e.g. due to differences in standard of care) or because of different research questions within the complete approved indication of a specific treatment (e.g. due to different lines of therapy), it is possible that more than one PICO is required to define the research questions to be answered in a given assessment. In this document, an individual set of PICO elements which together define a research question is called a PICO question. Thus, within a given assessment there might be the need to elaborate on one or more PICO questions.

In several countries the assessment of the complete approved indication of a new pharmaceutical intervention is required. Therefore, the PICO question(s) should always cover the complete suggested (and finally approved) indication for pharmaceuticals. The situation for other technologies is more complex, therefore, the question how broad the indication covered by the PICO needs to be has to be decided on a case by case basis.

3.3 *Use of the PICO in the assessment*

The translation of the policy question into a research question via a PICO helps to specify the data requirements and the framework for the assessment.

3.3.1 *Data requirements*

Currently, EUnetHTA has several options for an assessment with regard to information retrieval:

- to perform an assessment based on an evidence submission by a (prospective) marketing authorisation holder (pMAH)/manufacturer

- to perform an assessment based on an own information retrieval by the EUnetHTA authoring team.
- to perform an assessment based on a mixed information retrieval, i.e. based on an evidence submission by a (prospective) marketing authorisation holder (pMAH)/manufacturer which is supplemented by evidence from an own information retrieval by the EUnetHTA authoring team

The PICO questions specify the data requirements for all types of approaches.

Once the PICO questions are defined, they also determine eligibility criteria (for the individual components defined in the PICO questions) for studies or data to be included in the assessment. Inclusion criteria based on the PICO questions may be supplemented by additional criteria like study type or duration of study. These additional criteria are outside the scope of this document. Inclusion and exclusion criteria should be reported in the methods section of the project plan.

If the available studies as such do not meet the requirements of the PICO questions there are various methodological options to approach an assessment of the research question specified by a PICO. In addition to inclusion of complete studies, subsets of data from studies (e.g. subpopulations meeting the population definition from the PICO question) could be relevant for an assessment. If no direct comparisons of the intervention and comparator specified in a PICO question are available, the requirements of the specific PICO might also be approached by appropriate indirect comparisons. All these options stand under the reservation of the use of consolidated EUnetHTA methodology.

For assessments involving evidence submission by (p)MAHs/manufacturers the PICO questions and thus the resulting data requirements are communicated to the (p)MAH/manufacture to enable a data submission that meets the requirements of the assessment.

3.3.2 Framework for the assessment

In the assessment the data are included, presented and assessed according to the PICO question(s).

In case of assessments based on an evidence submission by a company, it is checked if the submitted evidence meets the requirements of the PICO question(s). If the assessment includes evidence based on an own information retrieval by the EUnetHTA authoring team it is checked if the evidence identified by the search meets the requirements of the PICO question(s). This also includes an evaluation of whether any deviations from the PICO question(s) in the available evidence (e.g. in the included patient population) means that a study or data set still allow for any conclusions with regard to the PICO question(s) or whether the data cannot be used in the assessment of the PICO question(s) (and the resulting gaps are described in the evidence gap table).

The evidence relevant with regard to a given PICO question is presented and assessed for an answer to the research question reflected by the PICO. The conclusions from the assessment are drawn according to the PICO question(s). This includes both the description of effects and evidence gaps.

The following figure presents an overview of the role of a PICO for EUnetHTA assessments.

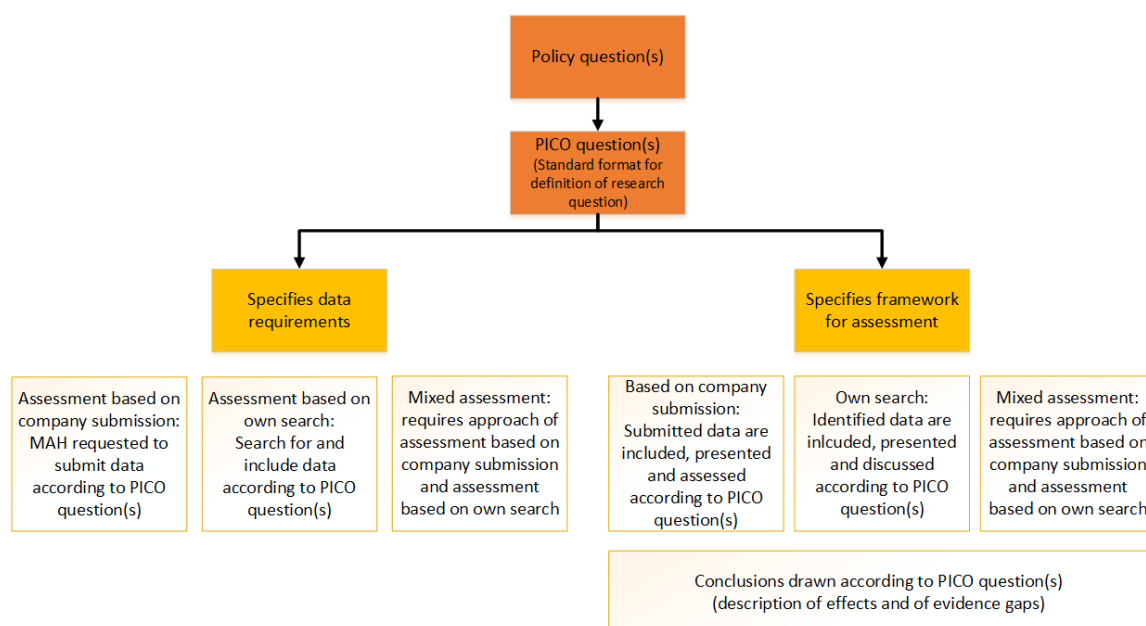


Figure 1 – Role of the PICO for EUnetHTA assessments

3.3.3 Additional study inclusion, presentation and assessment

In addition to the assessment according to the PICO questions(s) defined in the planning stage of the assessment, it might be an option to provide an assessment of the available studies or of certain studies (according to their originally planned methods), even if they do not meet the PICO questions(s), if this is needed by EUnetHTA partners. Examples could be studies in wider populations than defined by the PICO question(s) or studies with comparators which have not been included in the PICO question(s). This approach should also be decided in the planning stage of the assessment. If additional studies are presented and discussed in the assessment report, it should become clear from the report that this evidence is not addressing the PICO question(s).

4 DEFINE A STANDARD METHOD AND PROCESS ON HOW TO DEVELOP THE PICO QUESTION(S) FOR JOINT OR COLLABORATIVE ASSESSMENTS

In EUnetHTA assessments, there are two main phases: the scoping phase and the assessment phase. In PT, the scoping phase starts by receipt of the Letter of Intent, continues into the development of the final PICO question(s) by incorporating PICO survey results and ends with the publication of the final Project Plan (after CHMP opinion). For further details on the process, please refer to the appendix. In OT, the scoping phase starts as soon as the assessment team is established, continues into the development of the final PICO question(s) and ends with the publication of the final Project Plan. The use of a PICO survey will be piloted and based on experiences from the pilot, recommendations about its inclusion into the process will be made.

With the objective to define a standard method and process on how to develop PICO question(s) for Joint and Collaborative Assessments, the learning and experiences from prior pharmaceutical PICO-surveys are analysed. The pharmaceutical experiences will serve as a basis in designing the OT PICO survey methods and process as well. By means of the PICO survey, all partners have the opportunity to share their national needs. The aim of such PICO survey is to support the Authoring Team in developing PICO questions that are relevant for as many EUnetHTA partners as possible.

With *relevant* meaning that the included PICO question(s) cover as many partners individual PICO question(s) as possible in order to result in as less extra local assessment work as possible. However, at the same time it should not interfere with the national decision-making process (e.g. it should not rank outcomes because the relevance of outcomes will be determined in the national appraisal processes).

4.1.1 Prior experiences: the PICO survey

The PICO survey, was originally developed in July 2018 (for PT assessments) to meet the research needs of partners. By means of this so-called PICO survey, WP4 pharma aimed to get an early agreement of which aspects to be included in the assessment specific PICO(s). This survey was welcomed by the WP4 partners as well as the authoring teams and therefore was added as a standard process step in the scoping phase. The PICO survey is conducted via an online platform accessible to all partners. In OT, a PICO survey is yet to be piloted. It needs to be noted, that as of May 2020, there has been no single OT assessment which has been based on manufacturer submission dossier, nor on topic proposal from a manufacturer. This is not uncommon in OT assessments, therefore the only instance the manufacturer would/could give their input to the PICO question(s) is in the scoping (e-)meeting or if that is not done, in commenting on the preliminary PICO question(s). The preliminary PICO question(s) are established by the authoring team.

4.1.2 PICO survey; to investigate bandwidth and consolidate

PICO surveys were conducted for 11 pharma JA. All the prior surveys requested each and every partner to complete the survey, regardless of their role in the Assessment Team. Partners were also asked to indicate if the Joint Assessment was not relevant to them, so that the Authoring Team could understand why there is no input from a certain partner. Analysis shows that on average 14,6 partners (range: 11 - 17) were involved in the development of the PICO question(s), i.e. by replying to the PICO survey, or involved in assessment team, or having indicated that the topic is not of national relevance). **Figure 2** shows that the least discussion was about the proposed intervention while most discussion was around proposed Comparator(s) and Outcomes. This shows the divergence between partners on these PICO elements and stipulates the surplus the PICO survey has in establishing the range of PICO question(s).

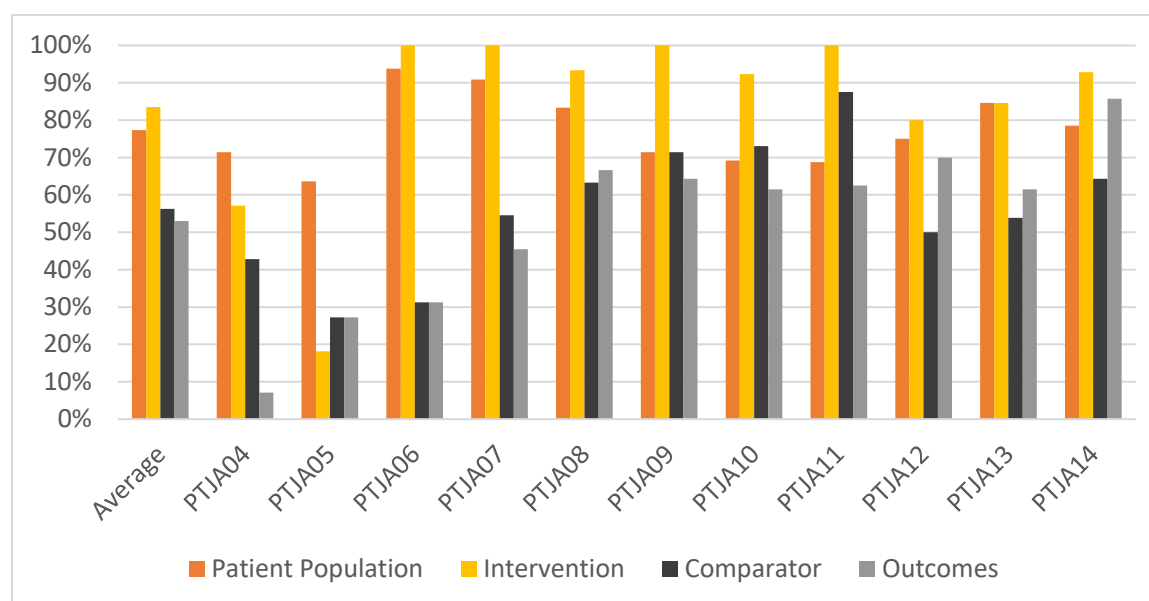


Figure 2 – Level of agreement Figure 2 shows the level of agreement on the different PICO elements.
Data cut-off: 03 April 2020

The added value of a PICO survey to establish and consolidate respective PICO elements is further confirmed by an analysis of the number of changes that were made on the original PICO question(s) brought forward by the authoring team. **Figure 3** shows the number of changes that were made to the different PICO elements, based on the PICO survey and on CHMP opinion¹. This figure confirms that the less agreement there was, the more changes have been made. Changes made to PICO elements encompass:

- Population: e.g. change of wording; adding/removing of subgroup
- Intervention: e.g. rephrasing; adding mode of action/dosage
- Comparators: i.e. adding and/or removing of comparators
- Outcomes: i.e. adding and/or removing of outcomes

¹ this is only applicable for the final PICO question(s). Final PICO question(s) means that the project plan is published. If the project plan is not published yet, there is no CHMP opinion available yet and the PICO question is considered preliminary.

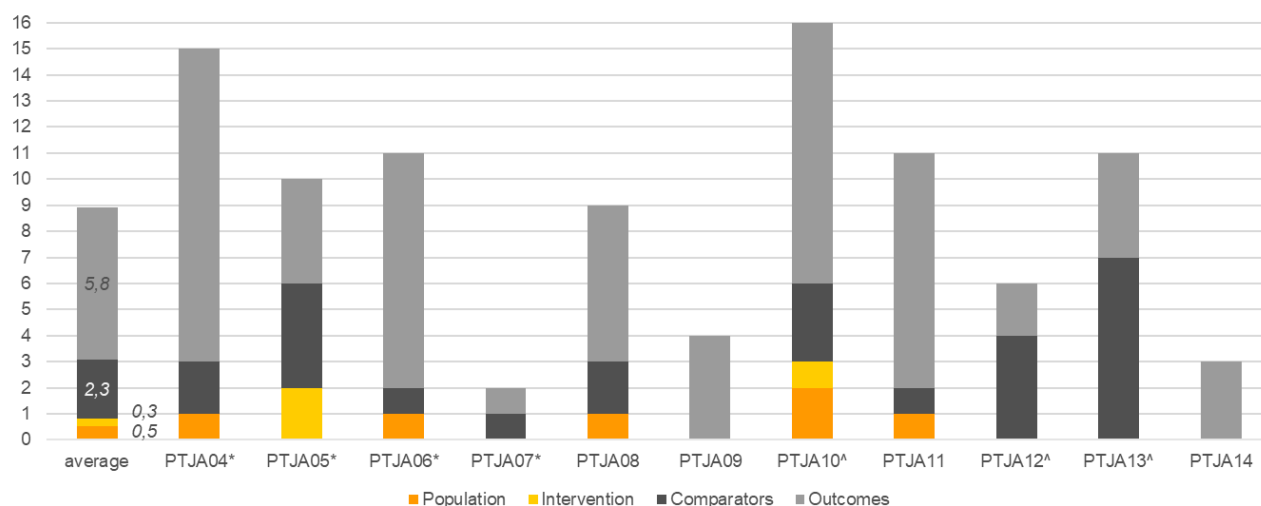


Figure 3 – Number of changes made after PICO survey

Data cut-off: 03 April 2020

Based on these analyses and the experiences from the authoring team, it can be concluded that the PICO survey is an appropriate process step in the development of EUnetHTA PICO question(s), to investigate the European range in PICO question(s) and consolidate the definitive PICO question(s).

For OT, the feasibility for a PICO survey is to be piloted, but also here the aim is to provide partners with reports that require as less extra assessment work as possible.

4.1.3 Further insights from prior pharma PICO surveys

Role (p)MAH

Looking back in EUnetHTA's history, with the first four PICO surveys the PICO question(s) as proposed by the (prospective) Marketing Authorisation Holder (pMAH) in the Letter of Intent (LoI) was used as a starting point to create the PICO survey. Soon, it was experienced that the proposed PICO question(s) by the (p)MAH did not well reflect the needs from EUnetHTA partners. Therefore, the subsequent PICO surveys were always based on a PICO question(s) developed by the Authoring Team. The Authoring Team can use the PICO question(s) proposed by the (p)MAH as a starting point, as for example for pharma the assessment is dependent on the claimed indication to the EMA. To date (April 2020), the PICO survey has been based on the authoring team's suggestion 7 times. This chimes with the assignment the assessment team has been given, to ideally base the PICO question(s) on the PICO requirements that the authoring team may have rather than to follow (p)MAH herein.

PICO Survey: endorsement and format

To ensure PICO input is relevant, the PICO input needs to reflect national needs and requirements. National needs are for example reflected in national medical guidelines. Some national agencies check the PICO survey with their national scientific committees or even with national clinical experts to ensure national relevance. Such a process endorses the national view on the PICO question(s). Furthermore, having an endorsed national PICO question(s) facilitates and speeds up national decision making, when a EUnetHTA report is published. For the authoring team to be able to incorporate each partners answers to the survey, it is mandatory for partners to provide answers (and justifications) to all questions.

Implementing PICO survey results & Pre-scoping

Recently, all PICO survey respondents are also invited to join the pre-scoping meeting as observers. This meeting takes place prior to the scoping Face-to-Face (F2F) meeting but after the development of the PICO question(s) and incorporation of PICO survey results. In this meeting the Authoring Team describes step by step how they developed the PICO questions(s) and how they incorporated the PICO survey results. By joining as observers, the PICO survey respondents can further explain their needs or ask questions if they do not understand how their input was incorporated. Including PICO survey respondents to this meeting was found helpful in making decisions on a consolidated and relevant PICO

question(s). For further details on the scoping phase (e.g. process steps and timelines), please see the appendix.

4.2 Requirements for a successful PICO survey

Based on the analyses of prior PICO surveys and other lessons learned, the following requirements can be formulated for a successful PICO survey.

- The PICO question(s) for the survey should initially be developed by the Authoring Teams and should be based on their relevant policy questions (For PT: the claim / indication (targets "I(ntervention) on P(opulation)" to the EMA should be the basis for the "Population" and 'Intervention' of PICO. Source being the Letter of Intent as submitted by the (p)MAH. For OT: the indications for use as found in the regulatory approval should be the basis for the PICO question(s). If that is not available, the intended use as stated by the manufacturer or as found in guidelines should be used. With multiple PICO questions being proposed by the authoring Team, the authoring team also describes in the PICO survey how these PICO questions relate to each other.
- A national PICO survey response will be treated by the Authoring Team as a national position informed by the national policy question, unless regulated otherwise, e.g. by regional HTA organisations. It is suggested to partners to have a process in place to ensure national requirements affecting the PICO(s) are met. With multiple PICO questions and their relations being proposed and described by the Authoring Team, each partner should also comment as extensive as possible on the applicability of each PICO question (and relation) with respect to their national setting. This helps the Authoring Team to develop the final PICO question(s).
- A transparent and accountable process should be in place on how survey answers are handled and incorporated (or omitted) by the Authoring Team. The Authoring Team should provide (informal) responses to all survey answers and share the merged PICO survey results (including the answers of the authoring team) with the entire Assessment Team and with all PICO survey respondents.
- PICO survey respondents are part of the internal scoping e-meeting, and join the discussion around the decision making on the PICO question(s) and are free to ask follow-up questions or advocate for the importance of incorporating certain PICO survey results. Based on these discussions the Authoring team either complies and adjusts their initial PICO question(s) where necessary, or explains why certain requests could not be fulfilled.

An outline of the PICO process including survey and internal pre-scoping is depicted below in Figure 4.

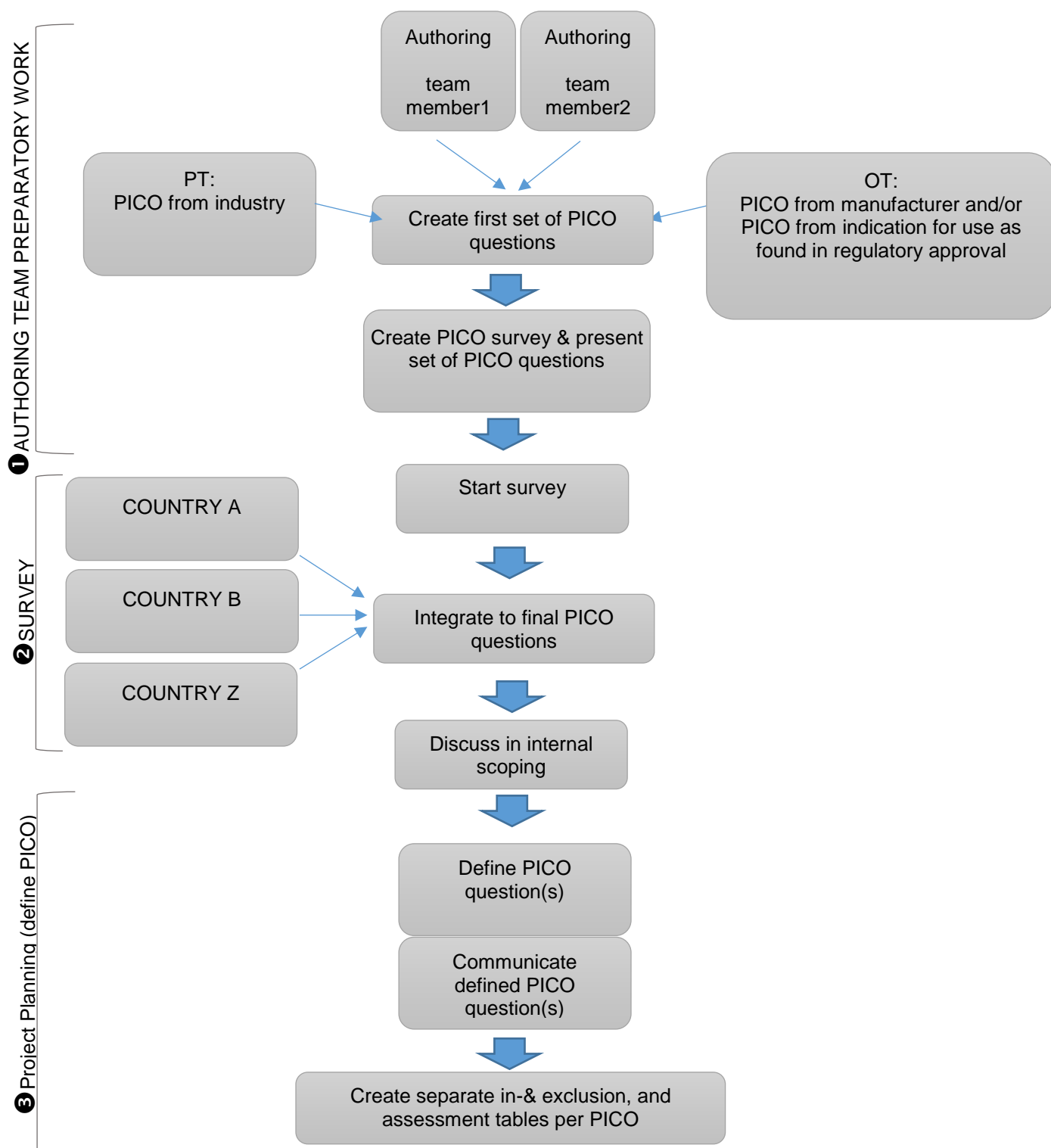


Figure 4 – Process steps for the development of the PICO question(s)

4.3 How to arrive at a comprehensive set of PICO questions

As can be seen in Figure 4, at two occasions the authoring team needs to create a set of PICO questions. At first on a small scale within the authoring team, and later on based on the input by EUnetHTA partners. Guiding principles for creating a set of PICO questions for EUnetHTA are the following;

- The PICO question(s) for the survey would be based on the assessment team national policy question and should not be merely based on the proposal of the manufacturer. The process of developing the PICO question(s) should be similar for PT and OT; should there be the need for any exceptions they can be made and explained
- PICO question(s) should aim to be relevant to as many partners as possible:
 - The final set of PICO question(s) should adhere to the MIN-MAX principle, i.e. with as small a set of questions as possible, serving as many partners' needs as possible.
 - The report should result in as less extra local assessment work as possible
 - The PICO should not interfere with the national decision-making process (e.g. it should not rank outcomes because the relevance of outcomes will be determined in the national appraisal processes).

The third principle has as a first consequence that, in order to adhere to the MIN-MAX principle, multiple PICO requests should be integrated as much as possible with consideration of the national needs. For this, it is essential to consider the relationships between multiple PICO questions. It is therefore needed that each country indicates upfront (at PICO survey stage) not only what they consider to be a relevant PICO question for their own country but also comment on the applicability of other PICO suggestions by the Authoring Team. Careful questioning during PICO survey is needed to investigate how PICO questions can be grouped. Cochrane and GRADE have formulated some considerations for the MIN-MAX principle and provide examples (e.g. see https://handbook-5-1.cochrane.org/chapter_5/5_defining_the_review_question_and_developing_criteria_for.html)

The third principle has as a second consequence, that on the basis of a EUnetHTA report all partners are enabled to follow their national process to an equal extent with as less extra local assessment work as possible. This principle applies as much to partners applying GRADE as to those which don't. The decision whether or not to follow GRADE in EUnetHTA assessments is dedicated to the Common Phrases and GRADE group. However, a method should be devised which serves both GRADE and non-GRADE national assessment processes without mutual impediment.

4.4 What to report in the Project Plan with regard to the PICO(s)

In planning a EUnetHTA assessment, there are some additional considerations the assessment team has to take into account besides what is required in a systematic review. EUnetHTA assessments follow a highly structured format and their preparation follows a structured process.

EUnetHTA assessments must have a written project plan, specifying in advance the scope and methods to be used, to assist in planning and reduce the risk of bias in the review process. EUnetHTA provides a structured format for both its project plan (PP) and assessment report to guide authors what they should report. The Project Plan for pharmaceutical (PT) and for other technologies assessments (OT) differ regarding their structure. We propose harmonisation but keeping separate templates for PT and OT due to specificities of both assessment types.

- The project plan includes the PICO question(s) resulting from the scoping phase. The template of the project plan should include a standard text explaining that the PICO question(s) reflect the needs of different partners based on their policy questions. For OT there might be projects where there is a need for a justification of the different PICO aspects.
- For each PICO question separate in/exclusion criteria should be provided in the project plan in the methods section (e.g. study design).

- Additionally, the project plan should state, in case of a PT assessment, that PICO survey is a standard process step (this is already present in the current template). In case of an OT assessment the project plan should state if a PICO survey was used and add some explanation what is the PICO survey. Ideally, the authoring team describes how the results of the PICO survey were taken into consideration in form of an informal internal document, which can be consulted later in case questions arise.
- It must be stated in the PP “If the PICO question(s) or the methods proposed in the PP are changed during the course of conducting the review, these changes should be documented and reported in “Deviations from project plan” section of the assessment report.” Potential deviations from the project plan could for example be triggered by new comparators that reach the market or a new patient group that has been recognized.

APPENDIX – PROCESS STEPS JA3 REAS

Process steps of the scoping phase PT

Figure 5 shows the current timelines of the scoping phase of a pharmaceutical Joint Assessment (PTJA). In PTJA, the scoping phase starts by receipt of the Letter of Intent, continues into the development of the final PICO(s) and ends with the publication of the final Project Plan (after CHMP opinion). Important milestones in the creation of the PICO(s) are:

1. Receipt Letter of Intent
2. Development of preliminary PICO for the PICO survey (based on PICO needs authoring team)
3. PICO survey & consolidation of results into 2nd draft PICO
4. Internal scoping e-meeting (referred to as pre-scoping e-meeting in the figure) to discuss the 2nd draft PICO with the entire assessment team and PICO survey respondents. The manufacturer is not invited to such meeting.
5. Scoping F2F meeting: this is important to hear whether there are any changes to the claimed indication to EMA anticipated
6. CHMP opinion: if the claimed indication to EMA changes, the PICO may also need to be adapted.

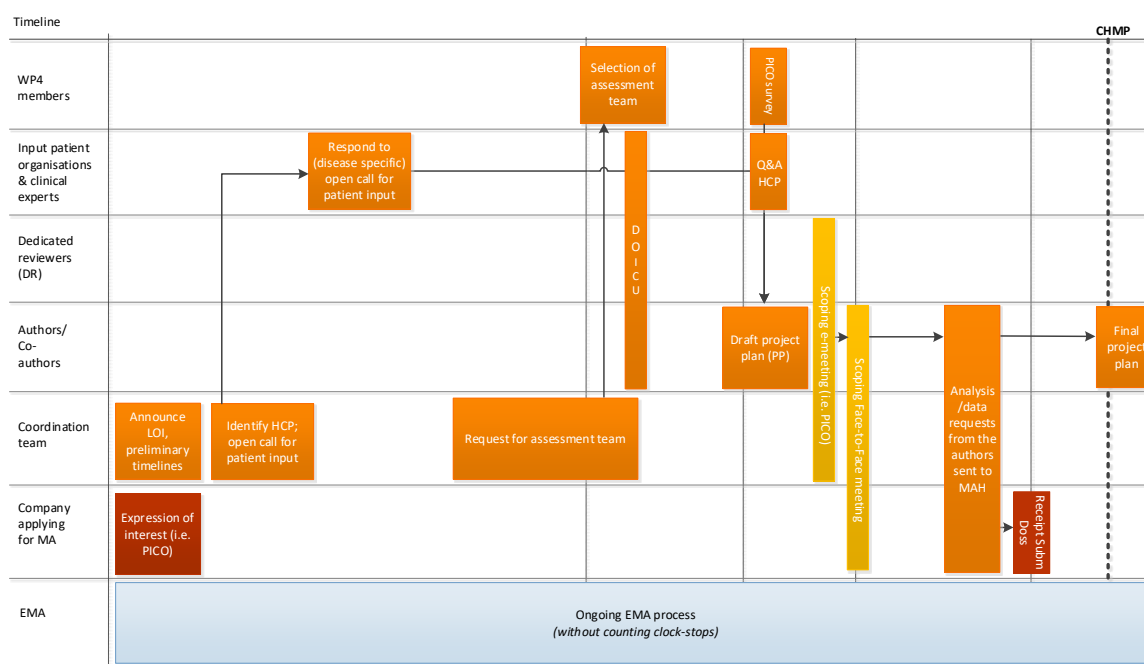


Figure 5 – scoping process steps pharmaceutical Joint Assessments

Process steps scoping phase OT

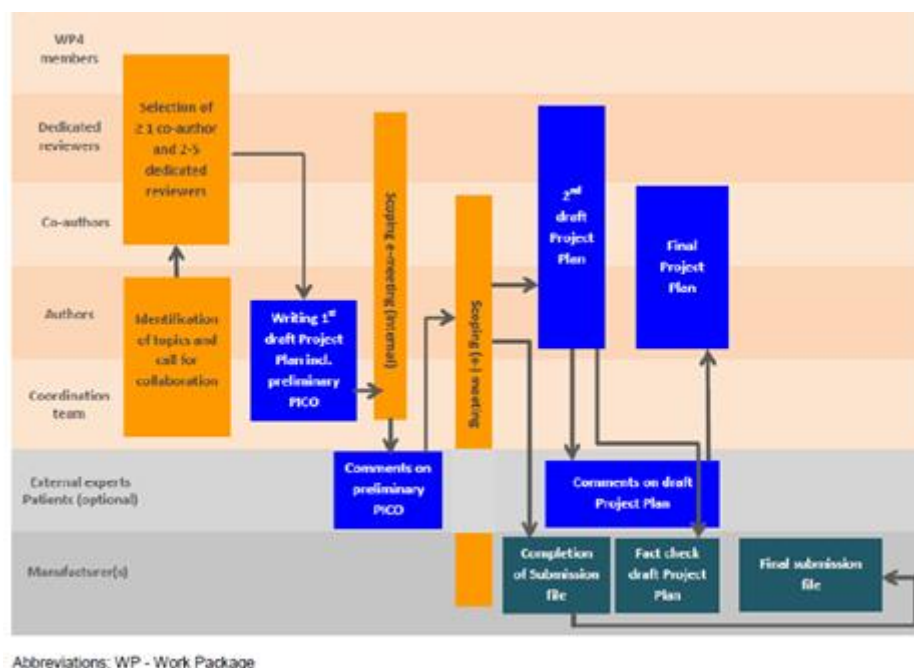


Figure 6 – Scoping process in Other Technologies Joint Assessments

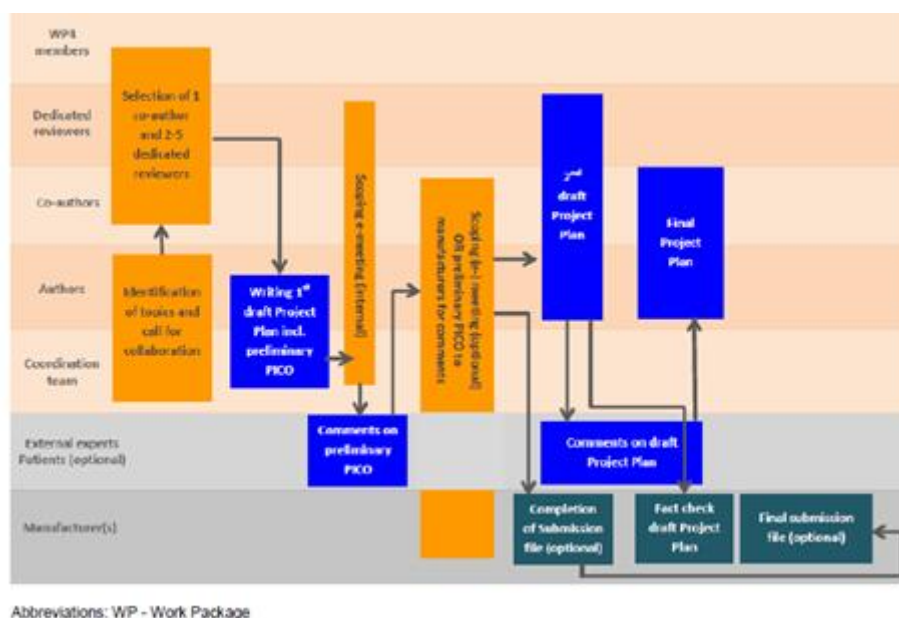


Figure 7 – Scoping process in Other Technologies Collaborative Assessments