EUnetHTA 21

Practical Guideline

D4.2 SCOPING PROCESS

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Disclaimer

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External Stakeholder Contribution

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Associated HTA bodies that reviewed the draft deliverable	
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LIST OF ABBREVIATIONS

BSC	Best Supportive Care
CE	Conformité Européenne
CHMP	Committee for Medicinal Products for Human Use
CSCQ	Committee for Scientific Consistency And Quality
EMA	European Medicines Agency
EU	European Union
HTA	Health Technology Assessment
HTAR	HTA Regulation
HTD	Health technology developer
JA2	Joint Action 2
JCA	Joint Clinical Assessment
JSC	Joint Scientific Consultation
SoC	Standard of Care
MD	Medical device (class IIb and class III)
MDCG	Medical Device Coordination Group
MS	Member State
PICO	Population, Intervention, Comparators, Outcomes

GLOSSARY

Best-Supportive Care (BSC)	Therapy ensuring the best possible, patient-individually optimized, supportive treatment to alleviate symptoms and improve health-related quality of life. "supportive" means that the treatment is not primarily causally addressing the given disease.
Comparators	Options against which the new health technology is compared, with the goal of determining if it provides additional benefits.
Individualized treatment	An individualized treatment is chosen for an individual patient by the physician from multiple available treatment options (all considered standards of care depending on patient characteristics). The choice is based on individual patient characteristics which should regularly be considered for the treatment decision (e.g. pre-treatment, severity of disease, general health status, localisation of tumor).
Policy question	The particular interest of a Member State considering the national context and health system, defining the assessment scope of a clinical assessment. The outcome of a clinical assessment and the national appraisal provide the answer to the policy question from the perspective of the Member State.
Subgroup	A subset of the study population defined by one or more specific patient characteristics (e.g. age, sex, mutations) measured at baseline. Subgroup analyses are performed to investigate potential effect modifications which are associated with these specific patient characteristics. The definition of subgroups will not lead to new PICO. Subgroup analyses are performed within a given PICO.
Subpopulation	A subset of the patient population covered by the therapeutic indication. The definition of subpopulations during the scoping process results in separate PICOs for each subpopulation. Subpopulations can be defined in order to address different policy questions. Potential reasons to define separate subpopulations, i.e. separate PICOs for each subpopulation, are: - the therapeutic indication explicitly comprises different subpopulations, e.g. defined by certain tumor entities, - different comparators are deemed appropriate for the subpopulations, - different prognosis of the subpopulations and therefore different effectiveness is expected.
Watchful waiting	Status in which there is no indication for a therapeutic intervention, neither for a causal treatment nor for a symptomatic or supportive treatment unless symptoms appear or change.

1 INTRODUCTION

1.1 The assessment scope

The basis of a Health Technology Assessment (HTA) is a set of defined research questions that are to be answered by the assessment and that together define the assessment scope. In the context of the European HTA, the assessment scope reflects policy questions from the different healthcare systems in which the HTA will be used. The PICO framework provides a standard format for specifying research questions, detailing the following parameters:

- P (population),
- I (intervention),
- C (comparator),
- O (outcomes).

For more details on the relevant policy questions and the PICO framework, see the PICO concept paper, which was developed in EUnetHTA Joint Action 3.[1]

According to Regulation (EU) 2021/2282 (HTA Regulation, HTAR), the overall assessment scope for the joint clinical assessment shall be inclusive and reflect Member States' (MS) needs [Article 8 (6)]. This means that the assessment should cover the PICO(s) requested by the MS.

1.2 Role of the PICO in the assessment

By principle, the scope of the assessment of an intervention should not be data driven, that is, the research questions should not be deduced from the available studies. Rather, an appropriate translation of national policy questions into research questions is performed during the planning stage of the assessment. This means that a particular research question (the PICO) is prespecified for a given assessment. As such, the definition of the PICO question(s) specifies the data requirements. For an assessment that is based on a submission by a health technology developer (HTD), the PICO specifies the data requested from the HTD. Furthermore, the PICO question(s) specify the framework for the assessment (Figure 1-1).

[1] https://www.eunethta.eu/pico/

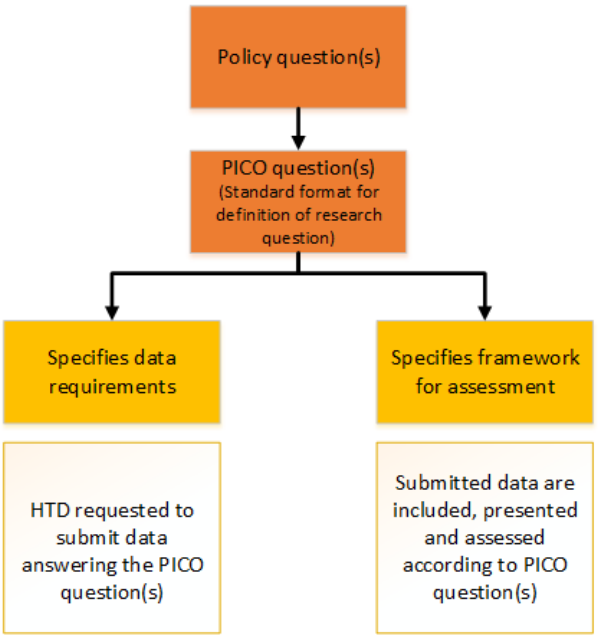

Figure 1-1: Role of the PICO in the assessment

HTD=health technology developer; PICO=Population, Intervention, Comparators, Outcomes.

1.3 Definition of the PICO(s) for an assessment

The PICO(s) for an assessment is defined during the scoping process. The scoping process is initiated by the Joint Clinical Assessment (JCA) secretariat according to the timeframe for, and well in advance of, the JCA. The aim of the scoping process is to identify the relevant PICO(s) for the assessment scope. As mentioned above, according to Regulation (EU) 2021/2282 [Article 8(6)], the assessment scope should be inclusive and reflect the MS needs.

To collect information about the MS needs, a PICO survey is conducted among the MS in which the MS provide information about their needs in terms of the PICO parameters (Section 3.1 PICO survey). To minimise the number of PICO(s), the assessor and co-assessor consolidate the PICO(s) as much as possible. Depending on the MS needs, the assessment scope can comprise one or more PICO(s) (Section 3.2).

The final assessment scope is provided to the HTD. It defines the data request for the assessment and enables the submission of a dossier in principle meeting the needs of MS.

1.4 Relevant articles in Regulation (EU) 2021/2282

Articles from Regulation (EU) 2021/2282 directly relevant to the content of this practical guideline are:

- Article 8: Initiation of joint clinical assessments;
- Article 9: Joint clinical assessment reports and the dossier of the health technology developer;
- Article 10: Obligations of health technology developers and consequences of noncompliance.

Throughout this document, any mention of articles refers to this Regulation.

2 SCOPE AND OBJECTIVE OF THE GUIDELINE

The objective of this practical guideline is to support the assessor and co-assessor in developing the assessment scope by describing the methods and principal steps of the scoping process. It covers the process from setting up the PICO survey to informing the HTD about the PICO(s).

In addition, the guideline describes the data presentation considering the definition of PICO(s). Furthermore, the impact of the statistical analysis plan of the original study versus the PICO(s) on the evidence assessment in the HTA report is addressed.

3 THE SCOPING PROCESS

In EUnetHTA 21, the scoping process starts with submission of a request for assessment by the HTD and ends when the consolidated final PICO is communicated to the HTD. Figure 3.1 lists the steps involved.

3.1 The PICO survey

3.1.1 Objective of the PICO survey

The PICO survey provides the opportunity for each MS to identify and provide their national needs. It is the responsibility of each MS to ensure that their inputs during the PICO survey match their needs in terms of parameters and of the information, data, analysis, and other evidence to be submitted by the HTD [see requirements laid down in Article 8(6)].

3.1.2 Process for assessors` proposal for PICO survey

The process starts when a product is identified to be the subject of a JCA and therefore, a PICO(s) proposal is needed. To start the procedure, assessors need to be informed of the claimed therapeutic indication for that product.

Once the assessors receive the information on the claimed therapeutic indication for the product identified, they will:

- Identify relevant European guidelines in the disease area to have information on the natural history of the disease, available alternatives and relevant outcomes;
- Identify alternative guidance documents (if European guidelines are not identified for the disease area of the claimed therapeutic indication);
- Obtain clinical opinion, if possible.

Based on the information identified, the assessors should then propose the PICO question(s) required to answer a clinical/medical care question. Such PICO(s) proposal(s) should have background information, as per the PICO Background Document Template [see Appendix B].

A meeting between the assessor and co-assessor for the discussion of the first draft of the PICO proposal is anticipated. Once the assessors agree on the draft proposal, the JCA Secretariat shares the draft PICO proposal, with the justification and background information, with Member States (MS). The Secretariat also develops the survey, where MS identify and provide their national needs. MS need to identify which PICO(s) from the assessors` proposal fulfil their needs. If any adjustments are needed, MS should outline the required adjustment and provide the rationale behind it in the specific field in the survey. Further, MS can submit one or more additional PICO(s) and should provide a rationale behind it in the survey, when this is needed to fulfil their needs.

3.1.3 Available data for PICO survey

The questionnaire for the PICO survey takes into account information provided by the HTD [Article 8(6)]; that is, information on the intervention to be assessed and the indication for which the HTD applied in the regulatory submission dossier (in the case of medicinal products) or the intended use according to the conformity assessment [in the case of medical devices (MD)]. This information is to be provided by the HTD upon request, before the beginning of the scoping process. In the EUnetHTA 21 context, this will be requested by means of a letter of intent (LoI) submitted by the HTD to the EUnetHTA 21 secretariat and this information will be made available to the MS. Under the HTAR, the submission of the LoI is not a legal requirement. The process will be duly initiated by the Member State Coordination Group on HTA (HTACG). The process is still under development.

The MS will be made aware of any Joint Scientific Consultation (JSC) that might have taken place for the medicinal product or MD under assessment. However, JSC recommendations might no longer be applicable because of changes in the underlying conditions (intended therapeutic indication, dynamic

therapeutic landscape for comparators, etc.). The PICO for the assessment should be generated under the conditions existing at the time of the survey.

3.1.4 Format of the PICO survey

The PICO survey is conducted by the JCA secretariat via an online platform accessible to all MS. MS are expected to answer within approximately 2 weeks.

To meet the objective of the HTAR, which is an inclusive scope, all MS shall participate in the PICO survey.

3.1.5 Expected inputs to the PICO survey

The PICO survey asks the MS to express their PICO requirements based on the assessors` proposal and to submit one or more additional PICO(s), if the assessors` proposal does not fully cover the national needs of the MS. It is the responsibility of the MS to define the PICO parameters according to their national legal and procedural requirements. The inputs can be found in Appendix A.

Given that any specific request might broaden the scope and increase the workload of the European assessment, MS are asked to limit their requests to the extent necessary for their national decision-making.

During the scoping phase, inputs from EU patients and experts will be taken into account. The process of which is detailed in deliverable 7.2. Member States are encouraged to involve national patient and clinical experts in the scoping process.

Further explanation of each parameter of the PICO is given below.

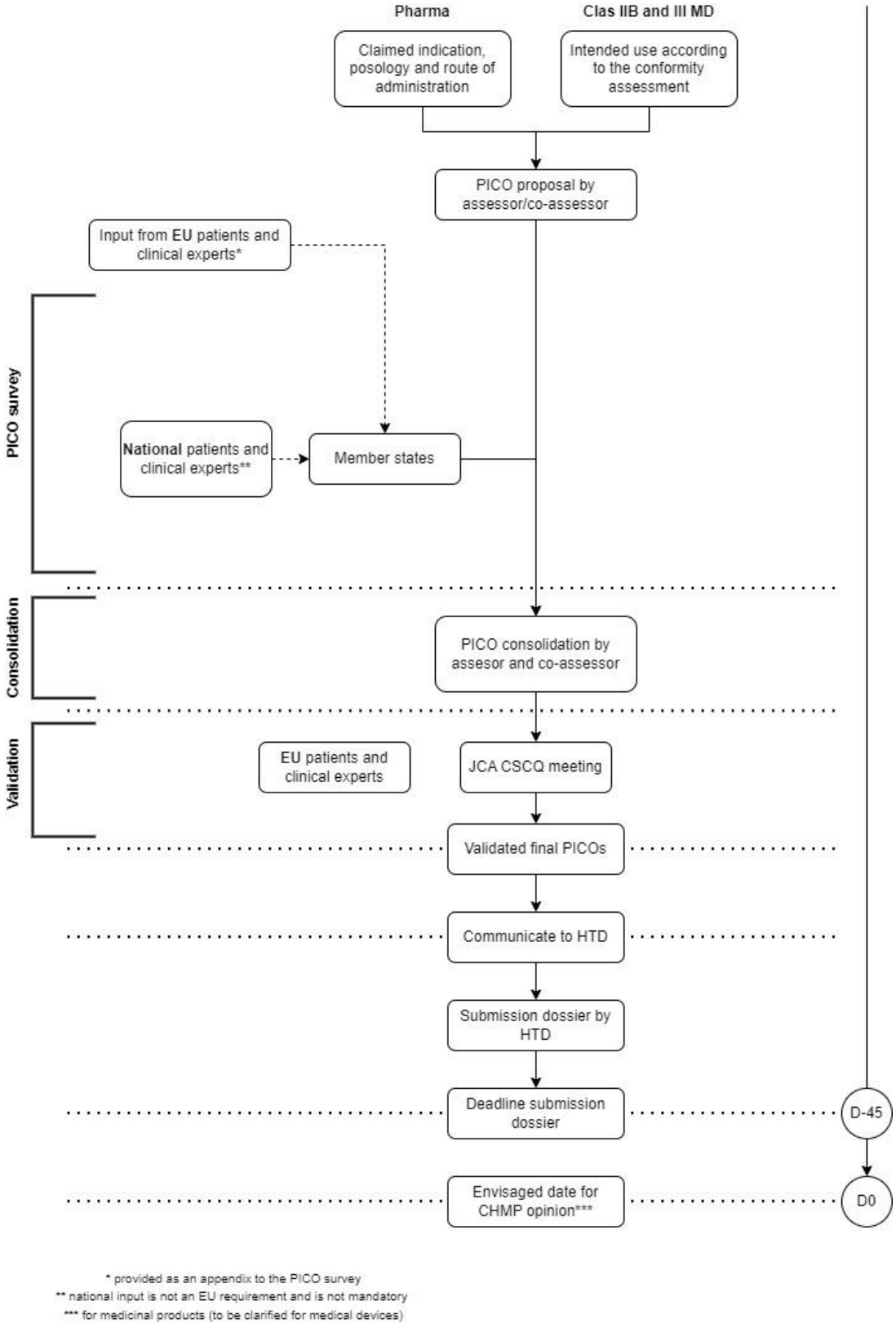

Figure 3-1: Steps for the scoping process

CHMP=Committee for Medicinal Products for Human Use; CSCQ=Committee for Scientific Consistency and Quality; EU=European Union; HTD=health technology developer; JCA=Joint Clinical Assessment; MD=medical device; PICO=Population, Intervention, Comparators, Outcomes.

In Figure 3-1 it is shown that there is only one timepoint specified (deadline for submission at the latest 45 days prior to the envisaged date of the opinion of the CHMP, for medicinal products), because it is

the only clearly defined in the HTA Regulation (Article 10(1)). Sufficient time should be allowed for the whole scoping process, including PICO survey and PICO consolidation.

Population

MS should identify the relevant population(s) for the assessment scope, based on the claimed therapeutic indication (i.e., indication applied for by the HTD in the submission to the EMA; in the case of medicinal products) or the intended use according to conformity assessment (in the case of MD) and their local healthcare situation. Relevant population(s) should be:

- the full patient population applied for by the HTD; and/or,
- subpopulation(s): defined as part of the full population.

The definition of the relevant population(s) should be as clear as possible and avoid ambiguity. During the PICO survey and in the JCA Committee for Scientific Consistency and Quality (CSCQ) meeting, definitions of the relevant populations should be discussed, where necessary. For example, in multiple sclerosis, the term 'relapsing multiple sclerosis' has been used to describe both relapsing remitting multiple sclerosis and patients with secondary progressive multiple sclerosis with superimposed relapses.[2,3] Therefore, MS should state in the wording of the patient population, the details of the covered patient population. The final definition is used throughout the scoping and assessment phases.

When appropriate, MS should define different subpopulations of the therapeutic indication, according to MS needs. Please see the glossary for the definition of the concept.

Intervention

The intervention in the PICO should reflect the intervention to be assessed and the indication for which the HTD applied in the regulatory submission dossier (in the case of medicinal products) or the intended use according to the conformity assessment (in the case of MD).

Intervention for medicinal products could be: monotherapy, combination therapy, with or without best supportive care, and so on. Typically, an assessment covers one intervention (a single medicinal product or a single MD or a specific combination of therapies). In some cases, a new intervention can be added to, instead of replacing, the standard of care (SoC). In these cases, the SoC comprises a background therapy, which could be not only a pharmacotherapy, but also a nonpharmaceutical intervention, such as psychotherapy, radiation, physiotherapy, or surgery. In rare occasions, this background therapy might differ from one MS to another. The MS should clarify whether this therapy should also be part of the treatment in the group receiving the comparator. In cases in which the MS highlights a specific background therapy in the PICO survey for the intervention, the assessor and co-assessor have to decide whether to include the background therapy in the intervention part of the PICO during the consolidation phase. Variations of the intervention, such as dose or timing of administration, are potential effect modifiers and, as such, do not require a separate PICO.

Characteristics of the MD should be specified listing the device configurations/variants. However, different versions of the MD could impact effectiveness, and this should be considered.

Comparators

MS are expected to define the comparators to be used with each patient population they have requested. Comparators can be licenced or not in the European Union.

2 https://www.eunethta.eu/wp-content/uploads/2020/03/PTJA08-siponimod-final-assessment-report-v2.0.pdf?x16454

3 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-multiple-sclerosis_en-0.pdf

A SoC is an agreed standard treatment in a given health care system. As such, simply naming "SoC" as a comparator in the PICO survey is not sufficient. The components of SoC need to be specified for the given health care system to allow for the PICO consolidation.

Comparators are not limited to pharmacotherapy or MDs, but can as well include any other intervention, such as psychotherapy, radiation, physiotherapy, or surgery, or a combination of any of these.

If a comparator includes a specific background therapy, the MS should clarify whether this therapy should also be part of the treatment in the group receiving the intervention. A background therapy is a concurrent therapy that might be routinely applied, for example, as a SoC for a particular condition and/or disease.

The following figure gives an overview of potential comparator scenarios in a given patient population.

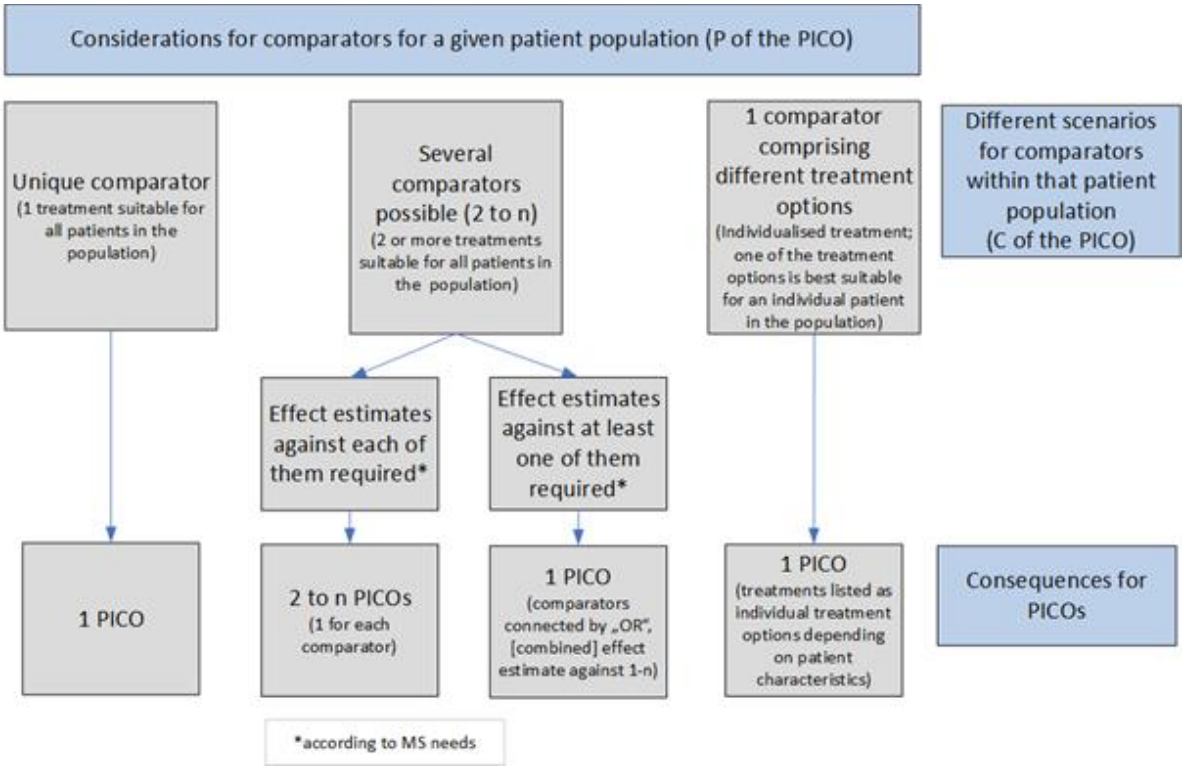

Figure 3-2: Considerations for comparators

There might be different scenarios for comparators within a given patient population.

If one unique comparator, which is suitable for all patients in a given population, is defined, a comparison (and thus effect estimates) against this one comparator is required. As shown in figure 3-2, this situation is reflected in one PICO.

If several comparators, which are all suitable for all patients in a given population, are defined, there can be two different situations.

1. A comparison (and thus, effect estimates) against each of these comparators is required.
2. A comparison (and thus, effect estimates) against at least one of these comparators is required.

In situation 1) a separate PICO is defined for each of the comparators. In situation 2) the different treatment options are combined in 1 comparator (treatments will be connected by "OR" to reflect the

situation) and 1 PICO comprising this comparator will be defined. The effect estimates could be provided against one or more of the treatments comprising this comparator. If more than one comparator is included, effect estimates should be provided for each comparator individually and aggregated for all comparators.

There might be situations in which a comparator, which is suitable for all patients in a given population, does not exist. This scenario will often be relevant for populations which are heterogeneous and do not have a well-defined evidence-based SoC. In this situation, treatments are often chosen from a compilation of different treatment options based on various patient characteristics, e.g. pre-treatment, the severity of the disease or the general health status. In this case, the comparator comprises these different treatment options and is called "individualised treatment". One PICO against the individualised treatment comparator will be defined. In this scenario, a comparison (and thus effect estimates) against the individualised treatment comparator is required. Depending on MS needs, the treatment options defined in an individualised treatment comparator may or may not be conclusive. The acceptability of the comparative evidence will anyway be concluded at national level as part of the appraisal process.

In theory, a patient population for which an individualised treatment comparator is defined, could be split into several subpopulations. For each of these subpopulations, one of the treatments comprising the individualised treatment comparator would be the most appropriate treatment. However, the individualised treatment comparator is chosen when the population cannot be split into a limited number of meaningful subpopulations. A decision about when to use different subpopulations and when to combine patient groups in one population with an individualised treatment comparator will need to be made at the point of the definition of the assessment scope.

Outcomes

"Outcome" is any concept that can be used for estimating treatment effectiveness, such as mortality, remission, disease control, function, health-related quality of life (HRQoL), symptoms and safety.

MS are expected to define their needs by listing several outcomes. Detailed guidance on choosing and appropriately defining outcomes during the scoping process can be primarily found in the EUnetHTA 21 D4.4 guideline "*Outcomes (Endpoints)*". Other guidance was developed in Joint Action 2 (JA2) [4,5,6,7,8]. Given that JCA reports should not contain any value judgement or ranking of health outcomes, the listing of outcomes for the assessment scope also should be free of any such judgement or ranking.

Additional information

MS could use this section to provide additional information for the assessor/co-assessor.

MS could request to explore potential effect modifiers within the population (i.e., by defining subgroups (see definition above) e.g., age, sex, dose).

[4] EUnetHTA (2015): Endpoints used for Relative Effectiveness Assessment: Clinical Endpoints. https://www.eunethta.eu/wp-content/uploads/2018/02/WP7-SG3-GL-clin_endpoints_amend2015.pdf

[5] EUnetHTA (2015): Endpoints used for Relative Effectiveness Assessment: Composite Endpoints. https://www.eunethta.eu/wp-content/uploads/2018/03/composite_endpoints.pdf

[6] EUnetHTA (2015): Endpoints used in Relative Effectiveness Assessment: Surrogate Endpoints. https://www.eunethta.eu/wp-content/uploads/2018/03/surrogate_endpoints.pdf

[7] EUnetHTA (2015): Endpoints used for Relative Effectiveness Assessment: Health-related Quality of Life and Utility Measures. https://www.eunethta.eu/wp-content/uploads/2018/01/Endpoints-used-for-Relative-Effectiveness-Assessment-Health-related-quality-of-life-and-utility-measures_Amended-JA1-Guideline_Final-Nov-2015.pdf

[8] EUnetHTA (2015): Endpoints used for Relative Effectiveness Assessment: Safety. https://www.eunethta.eu/wp-content/uploads/2018/03/WP7-SG3-GL-safety_amend2015.pdf

Specific requests made for additional information will be discussed on a case-by-case basis during the CSCQ JCA meeting.

3.2 PICO consolidation

After the different needs from MS have been collected through the PICO survey, the PICO consolidation phase serves to converge the variety of needs into a set of PICOs that specify the scope of the JCA and the data requirements to the HTD (for medicinal products and MDs).

The objective of the consolidation is to ensure that MS needs are translated in the lowest number of PICOs possible. One PICO comprises one population, one intervention (or combination), one comparator (which can include more than one intervention), and at least one outcome. The steps are explained below and are illustrated with an example. The consolidated PICO for CSCQ Review Template v1.0 [see Appendix B] is to be completed by assessors/co-assessors.

The example is designed to capture theoretically possible situations that might occur during consolidation.

To achieve the fewest PICO(s) possible during the consolidation phase, the assessors/co-assessors might contact the MS to clarify open questions resulting from the PICO survey and discuss options for consolidation. Especially if a specific PICO is only requested by one MS, this discussion might clarify the possibility to cover the need of this MS by one of the other PICOs.

3.2.1 Step 1: List the requirements per MS

For each MS, a table is populated with the requested population(s) per column. Each row indicates the requirements for the comparator(s). The first row concerning the comparators can be used to indicate whether the listed comparators are all required, or whether any one of those will suffice. The example is given for a medicinal product. For medical devices, the 'full licensed indication' can be read as 'full approved intended use'.

Example (hypothetical)

This example is chosen to illustrate a combination of scenarios (Table 3-1, Table 3-2, Table 3-3, Table 3-4).

Table 3-1: PICO of Member State 1

Member State 1	
Population(s)	Full licensed indication
	Comparator(s) Could use any of ~~/ all required~~
	Comparator 1
	Comparator 2

Explanation: this MS expressed a requirement for the assessment regarding the Full licensed indication only, and would require for this population either a comparison with Comparator 1 or a comparison with Comparator 2. This is what is called, in 'Comparators' (Subsection 3.1), an 'OR' situation.

Table 3-2: PICO of Member State 2

Member State 2			
Population(s)	Full licensed indication	Subpopulation A	Subpopulation B
	Comparator(s) Could use any of ~~/ all required~~	Comparator(s) Could use any of ~~/ all required~~	Comparator(s) ~~Could use any of /~~ all required
	Comparator 1	Comparator 1	
	Comparator 2		
	Comparator 3	Comparator 3	Comparator 3

Explanation: this MS expressed a requirement for the assessment regarding the Full licensed indication and Subpopulation A AND B. For the Full licensed indication, the MS would require a comparison with either Comparator 1 or Comparator 2 or Comparator 3. For the Subpopulation A, the MS would require a comparison with either Comparator 1 or Comparator 3. For Subpopulation B, a comparison with Comparator 3 would be required.

Table 3-3: PICO of Member State 3

Member State 3		
Population(s)	Subpopulation A	Subpopulation B
	Comparator(s) Could use any of ~~/ all required~~	Comparator(s) Could use any of ~~/ all required~~
	Comparator 1	
	Comparator 2	Comparator 2
		Comparator 3

Explanation: this MS expressed a requirement for the assessment regarding Subpopulation A and Subpopulation B (and not the Full licensed indication). For the Subpopulation A, the MS would require a comparison with either Comparator 1 or Comparator 2. For Subpopulation B, it would require a comparison with either Comparator 2 or Comparator 3.

Table 3-4: PICO of Member State 4

Member State 4	
Population(s)	Full licensed indication
	Comparator(s) ~~Could use any of~~ / all required
	Comparator 3
	Comparator 4

Explanation: this MS expressed a requirement for the assessment regarding the Full licensed indication only and would require for this population a comparison with Comparator 3 as well as a comparison with Comparator 4. This is what is called, in 'Comparators' (Subsection 3.1), an 'AND' situation.

3.2.2 Step 2: Create tables per population and juxtapose MS requirements

Set apart the required population(s) in separate tables and list in the columns all MS that require this population.

Add in the rows below their required comparator(s). Highlight whether the MS need either all of those or any of those comparator(s).

The first table has, by default, the (expected) licensed indication as the population.

Example (based on Tables 3.1–3.4)

Table 3-5: List of submitted comparators for the full indication (separated by Member State)

Full licensed indication		
Member State 1	Member State 2	Member State 4
Comparator(s) Could use any of ~~/ all required~~	Comparator(s) Could use any of ~~/ all required~~	Comparator(s) ~~Could use any of~~ / all required
Comparator 1	Comparator 1	
Comparator 2	Comparator 2	
	Comparator 3	Comparator 3
		Comparator 4

Table 3-6: List of submitted comparators for Subpopulation A (separated by Member State)

Subpopulation A	
Member State 2	Member State 3
Comparator(s) Could use any of ~~/ all required~~	Comparator(s) Could use any of ~~/ all required~~
Comparator 1	Comparator 1
	Comparator 2
Comparator 3	

Table 3-7: List of submitted comparators for Subpopulation B (separated by Member State)

Subpopulation B	
Member State 2	Member State 3
Comparator(s) ~~Could use any of /~~ all required	Comparator(s) Could use any of ~~/ all required~~
	Comparator 2
Comparator 3	Comparator 3

3.2.3 Step 3: Select, per population, the required comparator(s) and assign PICO(s)

The goal here is to select the lowest number of comparators needed to fulfil MS requirements.

a) One comparator: if a MS requires one comparator for a given population, this comparator is selected. This is done for all MS. Every different comparator is assigned a separate PICO.

b) More than one required comparator and the 'AND' scenario: for every additional required comparator, a separate PICO is assigned.

c) Select 'OR' comparators: if one or more MS require one comparator out of several options, check whether at least one of these comparators is included under steps a and b (see example below). If this is not the case, the list of comparators is crosschecked for all remaining MS for which this occurs. The lowest number of comparators needed to satisfy the requirements for MS will determine which comparators will be selected. If no preference can be given, this will be highlighted. In this case, the comparator definition will include the alternative options. This means that the HTD can choose the most relevant comparator from the options presented. Again, a separate PICO for every additional comparator scenario (in this case with alternative options) is assigned.

Example

Subpopulation B

Step a: One comparator

Only MS 2 requires only one comparator for a particular population; it requires Comparator 3 for Subpopulation B. This results in one PICO. With the inclusion of Comparator 3, the requirements of MS 3 for Subpopulation B are also satisfied. The needs of MS with regard to Subpopulation B are fulfilled with the selection of Comparator 3. Therefore, a PICO with Comparator 2 is not necessary and will not be included.

Full licensed indication

Step b: More than one required comparator and the 'AND' scenario

MS 4 applies the AND scenario and requires two comparators (3 and 4 are both required). This results in two PICOs. MS 2 could use any of comparators 1, or, 2 or 3. Hence, with the selection of Comparator 3 to fulfil the needs of MS4, the needs of MS 2 are also fulfilled. However, with the selection of comparators 3 and 4, the needs of MS 1 are not fulfilled because this MS needs Comparator 1 or 2. Therefore, an additional PICO with either of these two comparators 1 or 2 needs to be constructed. For MS 3, the Full licensed indication is not requested.

Given that there is no preference for either a comparison with Comparator 1 or a comparison with Comparator 2 (MS 1 and MS 2 could both use any of those two), the HTD can decide which of those two comparators will be included in the submission.

Therefore, in total, this population requires three PICOs: two PICOs that cover the needs for MS 4 (comparators 3 and 4) and one PICO that covers the needs of MS 1. The needs for MS 2 are included in those PICOs.

Subpopulation A

Step c: Select 'OR' comparators

With Comparator 1, the requirements of both MS 2 and 3 are satisfied. This requires one PICO. In this situation, Comparator 2 and Comparator 3 are omitted during the consolidation process, unless one of the MS objects.

3.2.4 Step 4: Populate a PICO table with the results of step 3

1) Each PICO is placed in a separate column. The required comparators are placed in the row below.
2) The required outcomes are added in the row below the comparators. For this, the guidelines on the selection of outcomes should be followed.[9,10,11,12,13] In principle, all outcomes should be included for all PICOs.

Error! Reference source not found.3-3 summarises the four steps of the PICO consolidation process. Applying these four steps should result in the smallest possible number of PICOs that meet the needs of MS (called the MIN-MAX principle in the PICO concept paper). After applying these four steps, whether the needs of MS are indeed met should be checked. In the example, crosschecking the PICO table below (Table 3.8) with the hypothetical PICO survey results as populated in step 1 shows that this is indeed the case. The PICO table is the end product of the PICO consolidation and can be used for further reference in the scoping and assessment process.

[9] EUnetHTA (2015): Endpoints used for Relative Effectiveness Assessment: Clinical Endpoints. https://www.eunethta.eu/wp-content/uploads/2018/02/WP7-SG3-GL-clin_endpoints_amend2015.pdf

[10] EUnetHTA (2015): Endpoints used for Relative Effectiveness Assessment: Composite Endpoints. https://www.eunethta.eu/wp-content/uploads/2018/03/composite_endpoints.pdf

[11] EUnetHTA (2015): Endpoints used in Relative Effectiveness Assessment: Surrogate Endpoints. https://www.eunethta.eu/wp-content/uploads/2018/03/surrogate_endpoints.pdf

[12] EUnetHTA (2015): Endpoints used for Relative Effectiveness Assessment: Health-related Quality of Life and Utility Measures. https://www.eunethta.eu/wp-content/uploads/2018/01/Endpoints-used-for-Relative-Effectiveness-Assessment-Health-related-quality-of-life-and-utility-measures_Amended-JA1-Guideline_Final-Nov-2015.pdf

[13] EUnetHTA (2015): Endpoints used for Relative Effectiveness Assessment: Safety. https://www.eunethta.eu/wp-content/uploads/2018/03/WP7-SG3-GL-safety_amend2015.pdf

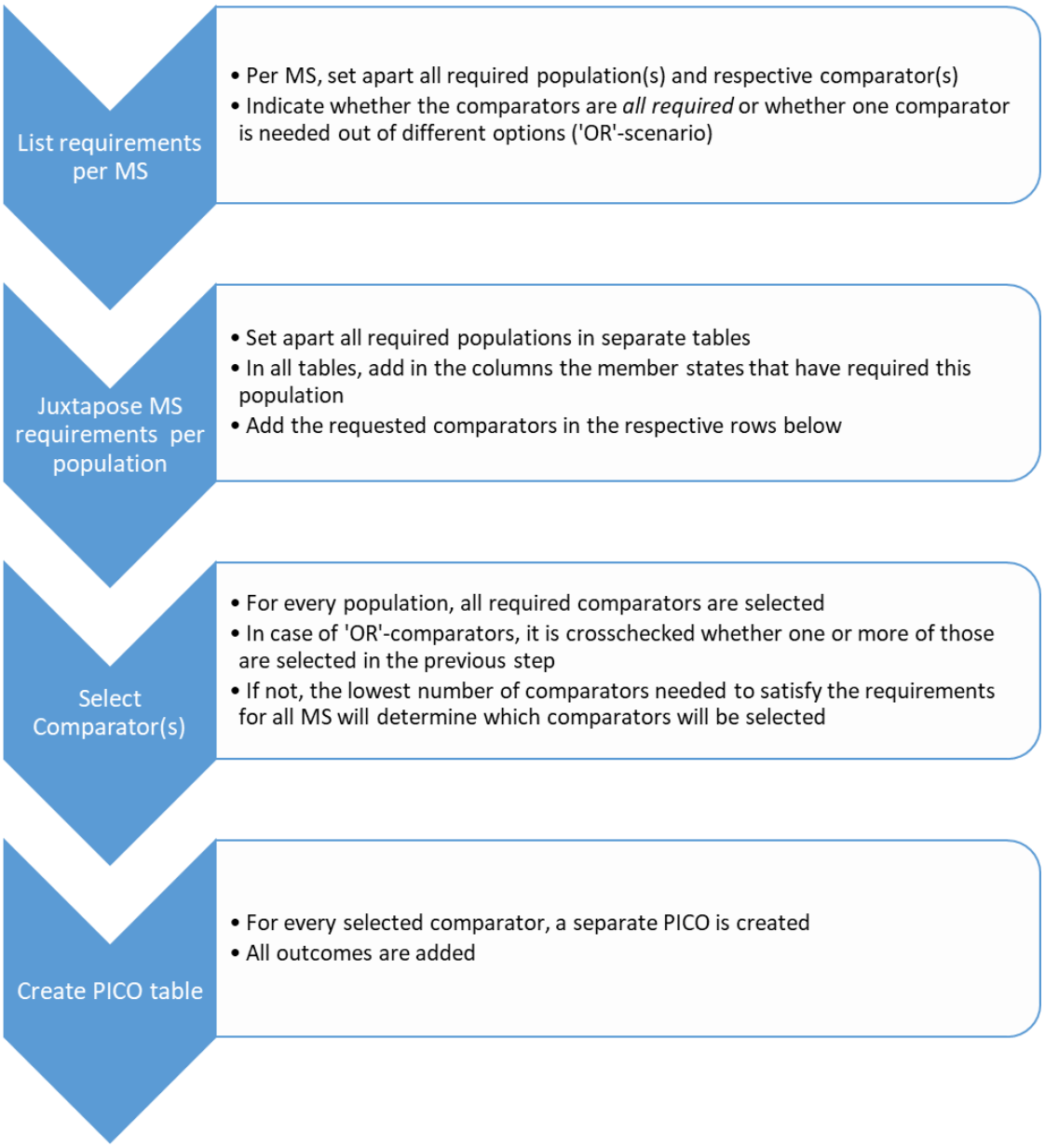

Figure 3-3: The four steps of the PICO consolidation process

Example (based on Tables 3.1–3.7)

Table 3-8: Consolidated PICOs based on Member State requests

	PICO 1	PICO 2	PICO 3	PICO 4	PICO 5
P	Full licensed indication	Full licensed indication	Full licensed indication	Subpopulation A	Subpopulation B
C	Comparator 1 OR Comparator 2[14]	Comparator 3	Comparator 4	Comparator 1	Comparator 3
O	All outcomes	All outcomes	All outcomes	All outcomes	All outcomes

3.3 PICO validation: CSCQ JCA meeting

PICOs resulting from the PICO survey as consolidated by the assessor and co-assessor are presented to the CSCQ JCA meeting. This presentation could take place during a programmed JCA CSCQ meeting or during a dedicated meeting, if timelines dictate. During this meeting, the assessor and co-assessor present the PICOs, including results of the survey, consolidation tables, and the proposal for consolidated PICOs. Cases in which a PICO was requested by one MS only will be discussed. CSCQ members as well as patients and clinical experts are invited to comment on the consolidated PICOs. However, a consensus should be reached that respects MS requirements because this requirement is determined by Article 8(6). CSCQ members should validate the final PICOs. The Final Consolidated PICO Template v1.0 should be completed with the validated PICOs and forwarded to the HTD.

3.4 Risk of labelling/CE marking indication(s) change

Given the timelines of the JCA, the scoping process has to be completed before Committee for Medicinal Products for Human Use (CHMP) opinion/Conformité Européenne (CE) marking indication(s). This means that the anticipated population might change after the PICOs have been postulated because of the regulatory process.

If CHMP opinion/CE marking recommends a different indication/intended use from the one initially applied for, an update of the PICOs is expected and the evaluation process will be delayed. A solution is needed to account for the risk of labelling change.

In the future HTAR, cooperation between the assessor/co-assessor and the corresponding regulatory team, according to Article 15(1), is planned and it should be explored whether this could contribute to a solution. In EUnetHTA 21, similar cooperation, although encouraged, could be more difficult to achieve because of the lack of a legal framework with the European Medicines Agency (EMA) and the Medical Device Coordination Group (MDCG).

[14] The HTD can decide which of those two will be included in the submission.

4 INFORMATION FOR THE HTD

Once PICO consolidation is completed and the scope of the assessment is validated by the CSCQ, the HTD is informed of the scope and the PICO(s) included. This scope defines the data request for the assessment. The HTA submission dossier should cover this data request.

5 DATA PRESENTATION IN THE HTA REPORT CONSIDERING THE PICO(S)

The PICO consolidation as explained in Subsection 3.2 has consequences for data presentation in the JCA. From the above, it follows that more than one PICO per population can be created in cases where there is more than one comparator brought forward by MS. For the JCA, all PICOs relevant for a single population can be clustered into one chapter in the report. Each relevant comparator is then assessed sequentially. Thus, the JCA comprises different chapters of assessments structured by population. In case of the situation as illustrated in Example 1 (above), this would result in three chapters: Chapter 1, Full licensed indication (medicinal product) or full approved intended use (medical device); Chapter 2, Subpopulation A; and Chapter 3, Subpopulation B, as illustrated by the example in Figure 5-1.

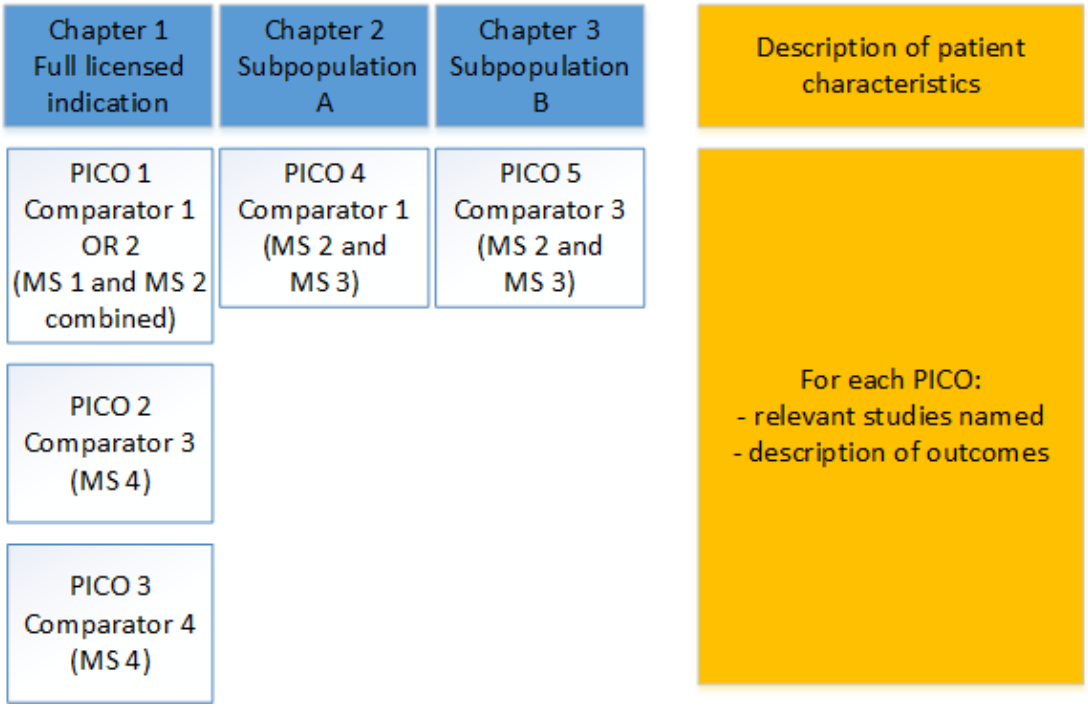

Figure 5-1: Data presentation according to PICO(s).

MS, Member State; PICO=Population, Intervention, Comparators, Outcomes.

Each population or subpopulation then constitutes a chapter in the report, and each comparator requires a subsection thereof. Each chapter will start with a description of the population it covers and each subsection with the comparator it covers. For the example as presented in chapter 3 of this guideline, the report will constitute the following three assessment chapters: Full licensed indication (medicinal product) or full approved intended use (medical device); Subpopulation A; and Subpopulation B. Note that only the first chapter has three subsections because it encloses three different comparators (Comparator 3, Comparator 4, and Comparator 1 OR 2). In Chapter 3 of the example, Comparator 3 is used once again; thus, the description of this comparator can be copied from, or a reference can be made to, the first chapter.

Further consequences are that a situation might arise in which different PICOs use the same studies as a basis. To prevent duplication throughout the JCA, description of (elements of) studies that would otherwise be repeated again in each chapter will be described at the beginning of the result section, which should also include results of information retrieval and characteristics of the included studies (Annexe I, HTAR). In addition, the intervention is a common element to each of the assessment chapters; thus, again to prevent duplication across chapters, a chapter occurring before the assessment chapters can describe (common elements of) the intervention. Further detailing of the report structure and data presentation will form part of the EUnetHTA 21 template.

6 IMPACT OF THE STATISTICAL ANALYSIS PLAN OF THE ORIGINAL STUDY VERSUS THE PICO(S) ON THE EVIDENCE ASSESSMENT IN THE HTA REPORT

As described above, the PICOs are developed based on the national policy questions to be answered by the assessment. As such, they are not driven by the available studies. Nevertheless, in many cases, the studies available for the assessment might cover a specific PICO. However, there might also be cases in which the available studies do not reflect a given PICO. For example, the specific PICO might comprise only a subpopulation of the population included in a study available for the assessment.

To meet the data requirements for an assessment according to a specific PICO, the available studies might need to be reanalysed or evaluated for suitability for indirect comparisons to provide a data set suitable for the assessment. This analysis will deviate from the original study planning but is required for the HTA by the definition of the PICO. This deviation should be clearly mentioned. The re-analyses will be provided by the HTD in the submission dossier.

In the assessment report, it should be clear which data sets are from an analysis according to the original study planning and which are based on reanalyses resulting from PICO requests. In any case, the original study analyses will be included in the dossier.

7 FURTHER RELEVANT DOCUMENTS

- PICO concept paper (https://www.eunethta.eu/pico/)

8 CONSIDERATIONS FOR THE HTA REGULATION

The HTAR serves as the basis for this deliverable. Given the general framework of EUnetHTA 21, this guideline deviates in some steps from the processes defined in the HTAR, in particular:

- The cooperation between assessor/co-assessor and the corresponding regulatory team, according to Article 15(1) of the HTAR could not be explored during EUnetHTA 21;
- Some steps of the processes in the HTAR (Articles 7 and 10) could not be introduced, such as the coordination group, corresponding subgroups, or the role of the European Commission. Those will be defined later under the HTAR. This could affect, for example, the starting point of a PICO survey for MD;
- Much of the content of this document is applicable to both EUnetHTA 21 and the HTAR. Where relevant, the differences will be specified. However, the scope of this guideline is limited to the relevant functions in EUnetHTA 21 only, given that the task of the corresponding committees might differ.

Input from patient organisations or clinical experts should be considered in the future in relation to implementing the HTAR.

8.1 PICO consolidation working group (PC-WG)

To facilitate capacity building, optimise resources and ensure consistency in the process and outcome of PICO consolidation, EUnetHTA 21 recommends the JCA subgroup assess the value, relevance and feasibility of establishing a dedicated working group (WG) on PICO. This working group should be involved in checking the assessors' PICO proposal for clarity and consistency with previous PICO surveys. Further, the PC-WG should liaise closely with the authors of the JCA during the PICO consolidation process.

Decision making on final consolidation lies with the JCA SG, as they validate the final consolidated PICO(s). In case the PC-WG and the assessment team have remaining discussion points, the JCA SG should be involved in finalizing the discussion.

EUnetHTA 21 further recommends the PC-WG is centrally coordinated, but this is not yet included in the process description.

Please see figure 8-1 for the proposed work flow for this PC-WG.

8.2 Bilateral exchanges with the PICO survey respondents

MS can reach out to the PC-WG in case they have questions about the PICO survey completion. The PC-WG can reach out to the assessment team, in case the questions are content related.

It is important that the authors of the JCA and the recommended PC-WG liaise directly with individual PICO survey respondents, to clarify specific aspects of their submitted PICO. As shown in figure 8-1, it is recommended such bilateral interactions take place prior to a CSCQ (or under the HTAR it is the JCA sub group) validation meeting. These bilateral meetings can also be used to discuss possibilities to further consolidate national requests.

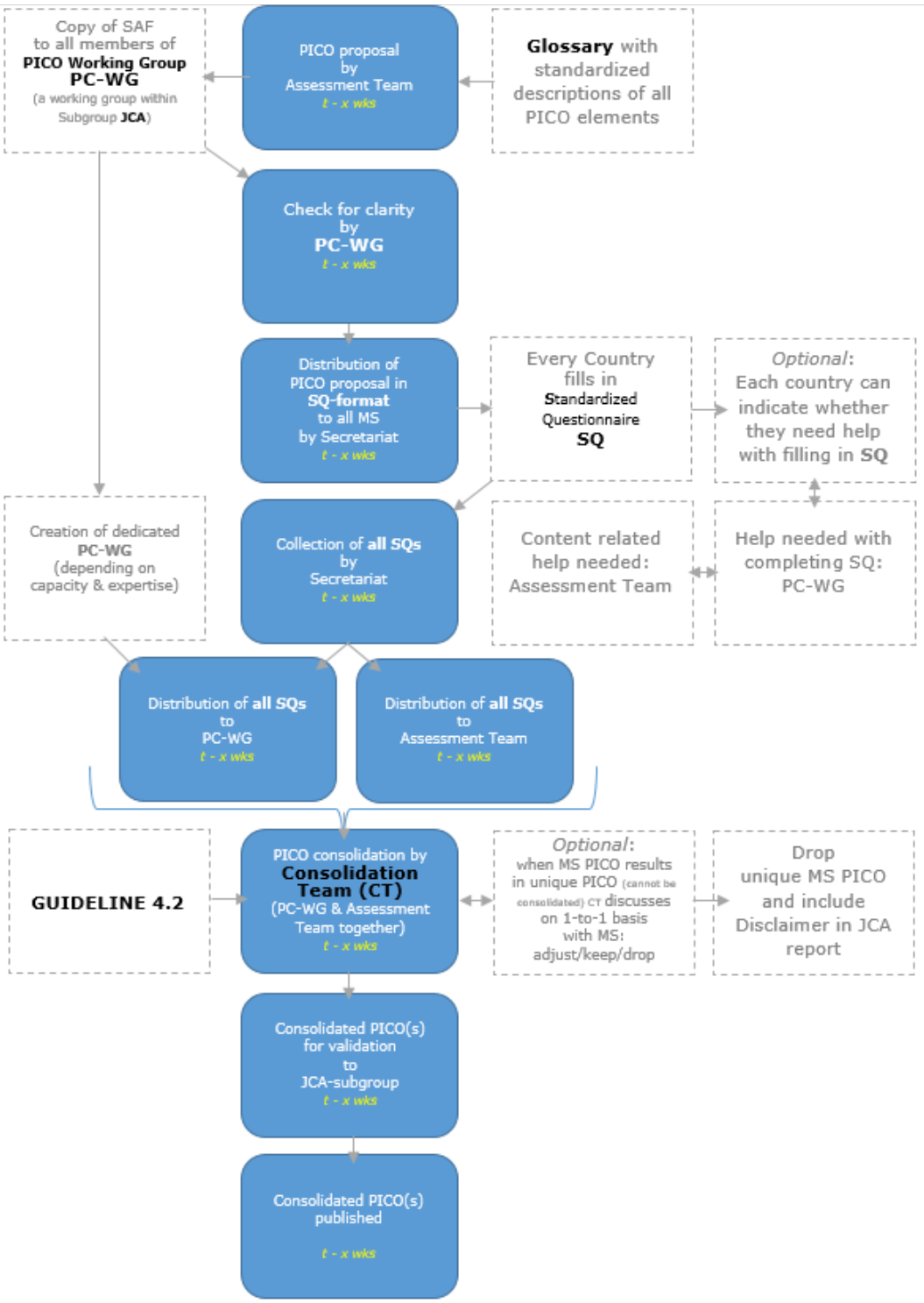

Figure 8-1: PICO work flow

8.3 Other recommendations

EUnetHTA 21 recommends producing a guideline explaining which data could be used to answer to a PICO. This guideline should detail the different PICO situations described in this current document. Such a guideline would be helpful to achieve completeness of dossier submission.

Appendix A - PICO SURVEY FORM

This is the PICO survey form for (intervention) in an (intended indication). This PICO survey provides the opportunity for each MS to identify and provide their national needs based on the assessors` PICO(s) proposal. Input provided during the PICO survey will be considered as the official standpoint of responding MS. Each MS has the full responsibility for its internal process (including the involvement of patients and clinical experts) to achieve this official standpoint. MS are expected to answer within 2 weeks.

Medicinal products JCA/high-risk medical device JCA PICO form

MS need to fill in each PICO parameter for each PICOs (in the case of multiple PICOs) or select an option from the assessors' proposal.

Parameter	**PICO 1 - Assessors´ proposal**	**Comment of MS to Assessors´proposal** *Agree, if MS- PICO is aligned with assessors´ proposal*	**Other PICO(s) (if needed)** *In case of multiple PICOs, separate columns should be made for the different aspects.* *If PICOs are aligned with regard to some parameters (e.g., no differences between the PICOs on outcomes), the cells should be merged between adjacent identical columns.*
Population	Relevant population for the assessment scope [see 'Population' (Subsection 3.1.5)]		
Intervention	Intervention to be assessed [see 'Intervention' (Subsection 3.1.5)]		
Comparator(s)	Expected comparators. [see 'Comparators' (Subsection 3.1.5)]		
Outcomes	Expected outcome (effectiveness, safety, quality of life) [see 'Outcomes' (Subsection 3.1.5)]		
Additional information	See 'Additional information' (Subsection 3.1)		

Appendix B – ADDITIONAL DOCUMENTS

The PICO Background Template Document v1.0 can be found here.

The Consolidated PICO for CSCQ Review Template v1.0 can be found here.

The Final Consolidated PICO Template v1.0 can be found here.