HTA CG | MEMBER STATE COORDINATION GROUP ON HEALTH TECHNOLOGY ASSESSMENT

Guidance on the scoping process

V1.0

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

List of abbreviations

Abbreviation	Definition
BSC	Best Supportive Care
CE	Conformité Européenne
CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
EU	European Union
HTA	Health Technology Assessment
HTACG	Member State Coordination Group on Health Technology Assessment
HTAR	HTA Regulation
HTD	Health Technology Developer
IA	Implementing Act
IVD MD	In Vitro Diagnostic Medical Device (class D)
JCA	Joint Clinical Assessment
JSC	Joint Scientific Consultation
MD	Medical Device (class IIb and class III)
MP	Medicinal Product
MS	Member State
PICO	Population, Intervention, Comparator(s), Outcomes
SG	Subgroup of the HTACG
SoC	Standard of Care

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Glossary

Term	Definition
Best-Supportive Care (BSC)	Therapy ensuring the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve health-related quality of life. "Supportive" means that the treatment is not primarily aimed at treating the disease but rather managing its symptoms.
Individualised treatment comparator	In a PICO for a given patient population, an individualised treatment comparator can be used when the standard of care for this population comprises multiple treatment options and the choice of a treatment from these options depends on on a patient's individual characteristics. Relevant characteristics are those which are regularly considered for the treatment decision in a given disease (e.g. pre-treatment, severity of disease, general health status, contra-indications, localisation of tumor). Individualised treatment consists of two or more treatment options.
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. For the purpose of JCA, policy questions pertain exclusively to the clinical domain and exclude e.g. health economic aspects.
Subgroup	A subset of the study population defined by one or more specific patient characteristics (e.g. age, sex, mutations, disease severity) 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 a new PICO. Subgroup analyses in the context of a JCA 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, could be: ▪ different comparators are deemed appropriate for the different subpopulations, ▪ the therapeutic indication explicitly comprises different subpopulations, e.g. defined by certain tumor entities, ▪ the subpopulations have different prognoses and therefore different effectiveness is expected.

Term	Definition
Watchful waiting	Status in which there is no indication for a therapeutic intervention, neither for a treatment aiming at curing the medical condition nor for a symptomatic or supportive treatment unless symptoms appear or change. Watchful waiting includes regular follow-up, according to the relevant health care context.

1 Introduction

1.1 The assessment scope

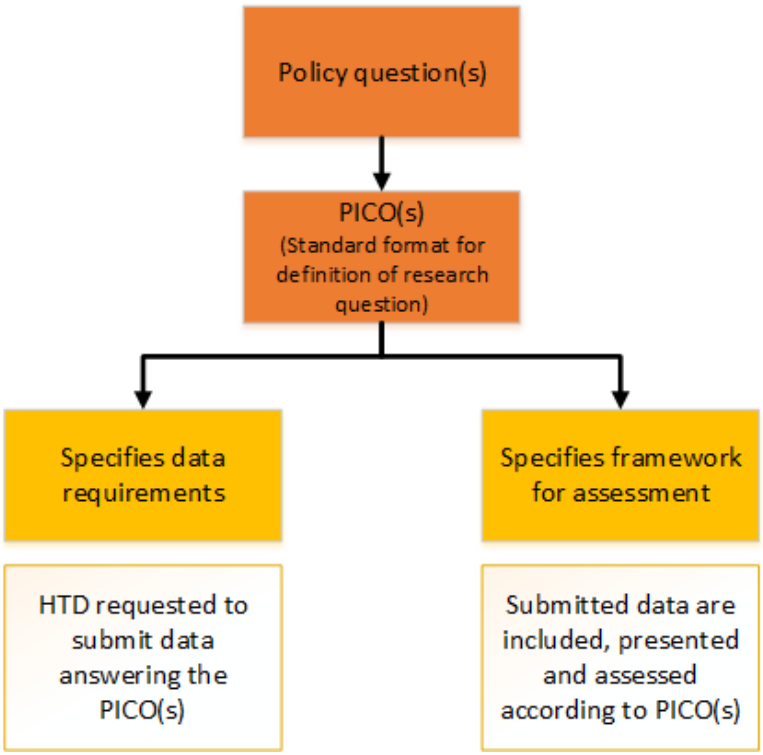
The basis of a Health Technology Assessment (HTA) is a set of defined research questions that are to be answered by the assessment and that together define the assessment scope. In the context of the Joint Clinical Assessment (JCA), the assessment scope reflects policy questions from the different healthcare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

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

According to Regulation (EU) 2021/2282 (HTA Regulation, HTAR), the overall assessment scope for the JCA *'shall be inclusive and reflect Member States' (MS) needs'* [HTAR 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

In general, the assessment scope is an appropriate translation of national policy questions into research questions. This means that a particular research question (the PICO) is prespecified (i.e. before the dossier is submitted) for a given assessment. As such, the definition of the PICO(s) specifies the data requirements. For an assessment that is based on a submission by a health technology developer (HTD), the PICO(s) specifies the data requested from the HTD. Furthermore, the PICO(s) specifies the framework for the assessment (Figure 1).



HTD: health technology developer; PICO: Population, Intervention, Comparator(s), Outcomes

Figure 1: Role of the PICO in the assessment

1.3 Definition of the PICO(s) for a joint clinical assessment

The PICO(s) for an assessment are defined during the scoping process, as described in this guidance. The aim of the scoping process is to identify the relevant PICO(s) for the assessment scope.

To collect information about the MS needs, a PICO survey based on an assessment scope proposal drafted by the assessor and the co-assessor[1] is conducted among the MS. By answering the PICO survey, the MS provide information about their needs in terms of the PICO parameters (Section 3.1 The PICO survey). The assessor and co-assessor consolidate the PICO(s) as much as possible (Section 3.2 PICO consolidation). Depending on the MSs' needs, the consolidated assessment scope can comprise one or more PICO(s) (Section 3.2 PICO consolidation).

According to HTAR Article 10(1): '*The Commission shall inform the health technology developer of the assessment scope and request the submission of the dossier (first request)*'. The assessment scope defines the data request for the assessment and enables the submission of a dossier designed to meet the needs of MS.

1 Key documents – European Commission

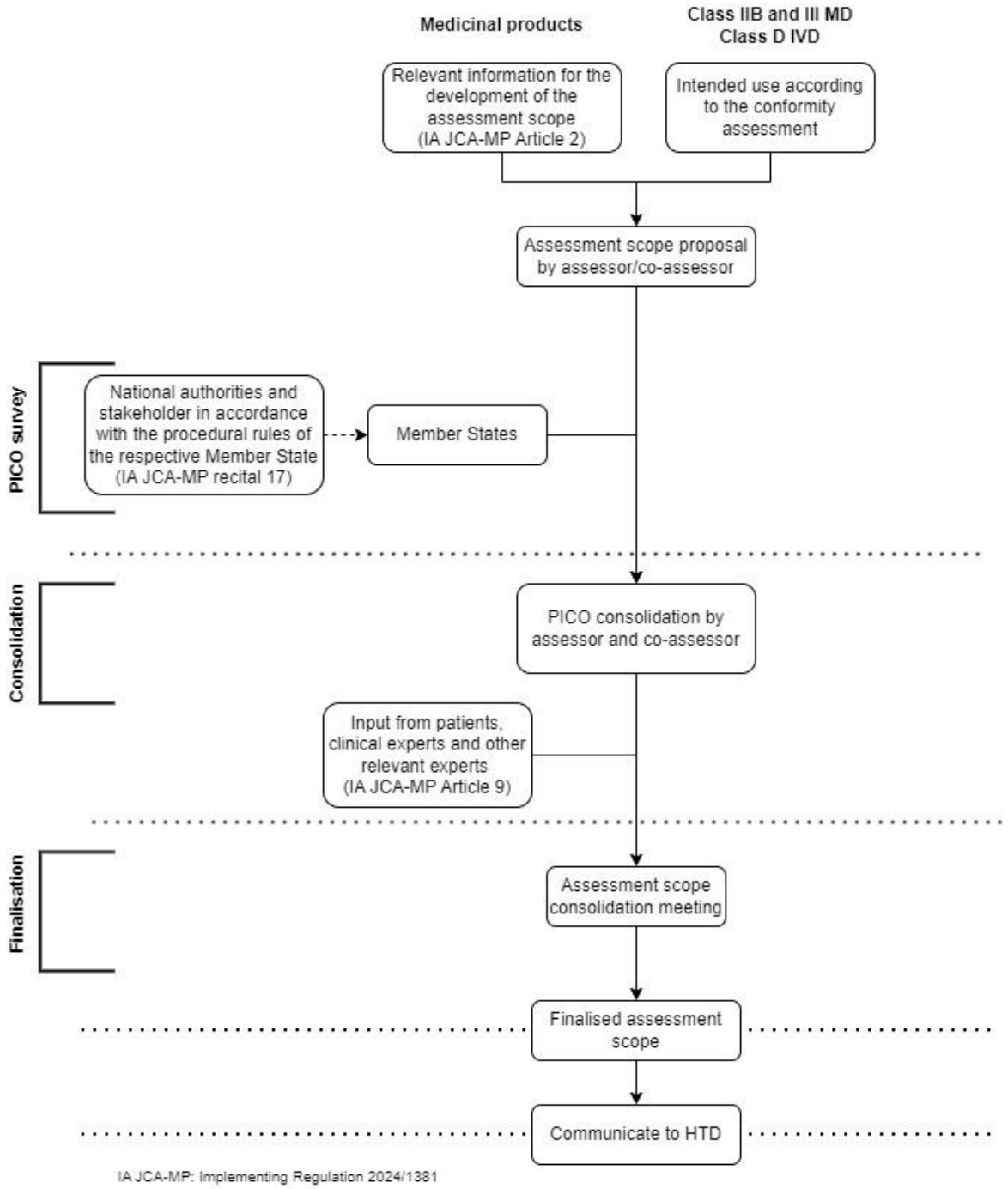
2 Scope and objective of the guidance

The objective of this guidance is to support MS for the preparation of the scoping process and for formulating their national PICOs, and 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 developing the assessment scope proposal for the PICO survey to informing the HTD about the PICO(s) of the assessment scope.

In addition, the guidance describes the data presentation considering the definition of the PICO(s). Furthermore, the impact of the statistical analysis plan of the original studies versus the PICO(s) on the evidence assessment in the JCA report is addressed (section 6).

3 The scoping process

The scoping process aims to define an assessment scope that reflects the MS needs. As such, the scoping process ends when the assessment scope is finalised. Figure 2 lists the steps involved.



HTD: Health Technology Developer; IVD: In Vitro Diagnostic Medical Device; JCA: Joint Clinical Assessment; MD: Medical Device; PICO: Population, Intervention, Comparator(s), Outcomes

Figure 2: Steps for the scoping process

3.1 The PICO survey

The PICO survey provides the opportunity for each MS to identify and provide their national needs.

3.1.1 Process for the assessment scope proposal for PICO survey

The process starts with the submission from the HTD of the relevant information specified in JCA IA-MP article 2 (Commission Implementing Regulation (EU) 2024/1381[2]) when submitting to the European Medicines Agency (EMA) (in the case of medicinal products [MP]). For medical devices (MD) or in vitro diagnostic medical devices (IVD MD), the corresponding IA[3] will provide the relevant information. The JCA SG should receive this information upon its receipt, as stated in JCA IA-MP article 4. National authorities and stakeholders should also receive this information according to a MS' national procedures (JCA IA-MP recital 17).

The assessor and co-assessor can then develop the assessment scope proposal based on the information received and other sources, including:

- Relevant European clinical guidelines in the disease area that provide information on the natural history of the disease, available alternatives and relevant outcomes;
- Alternative guideline documents (if European guidelines are not identified for the disease area of the claimed therapeutic indication/intended use);
- Input from the patients, clinical experts and/or other relevant experts (JCA IA-MP article 9(1).

As stated in IA JCA-MP Article 2(3): *'If the JCA Subgroup considers it necessary, the HTA secretariat shall invite the health technology developer to provide further information relevant for the development of the assessment scope in a meeting with the JCA Subgroup or in writing'*.

As stated in IA JCA-MP Article 8: *'At any time during the joint clinical assessment, the JCA Subgroup may seek input on the disease and therapeutic area from patient organisations, healthcare professional organisations or clinical and learned societies via the members of the HTA stakeholder network'*.

Assessor and co-assessor should also consult the joint scientific consultation (JSC) outcome document, if available, if there was a JSC for the health technology under assessment when preparing the assessment scope proposal.

2 Implementing regulation – EU – 2024/1381 – EN – EUR-Lex

3 The corresponding IA JCA-MD was not available while writing this guidance. The need for update will be discussed after the publication of the IA JCA-MD

Based on the information identified, the assessor and co-assessor should then propose the PICO(s) required to answer a clinical question (assessment scope proposal). The assessment scope proposal aims to support MS in responding to the PICO survey. Assessor and co-assessor should not include PICO parameters that may be specific or unique to their own MS in the assessment scope proposal. National requirements should be included in their own MS response to the PICO survey. The assessment scope proposal should rather include a minimum number of PICO parameters.

3.1.2 Available data for the PICO survey

The assessment scope proposal for the PICO survey takes information provided by the HTD into account [HTAR Article 8(6)]. For MPs this consists of *'the summary of product characteristics proposed by the applicant' and 'the clinical overview section of the submission file to the EMA'* [IA JCA-MP Article 2]. As stated in IA JCA-MP Article 2(3): *'If the JCA Subgroup considers it necessary, the HTA secretariat shall invite the health technology developer to provide further information relevant for the development of the assessment scope in a meeting with the JCA Subgroup or in writing'*.

For MD and IVD MD see the corresponding IA.

Relevant information can be made available via the JCA SG to MS for their national procedures (JCA IA-MP Recital 17). Where a JSC might have taken place for the MP or MD and IVD MD under assessment for the claimed indication/intended use, it is acknowledged that the JSC recommendations might no longer be applicable because of changes in the underlying conditions (intended therapeutic indication, intended use, dynamic therapeutic landscape for comparators, etc.). The PICO(s) for the assessment should be generated considering the situation prevailing at the time of the survey.

3.1.3 Format of the PICO survey

The PICO survey is conducted by the HTACG secretariat via the IT platform.

According to article 8(6) the HTAR, *'The assessment scope shall be inclusive and reflect Member States' needs in terms of parameters and of the information, data analysis and other evidence to be submitted by the health technology developer'*. To meet the objective of the HTAR, which is an inclusive scope, all MS will be invited to participate in the PICO survey. If MS choose to not participate in the survey, there is a risk their needs will not be covered by the JCA. There may also be health technologies which are outside the remit of HTA in a given MS. In this case MS should answer the survey accordingly.

3.1.4 Expected inputs to the PICO survey

The PICO survey asks the MS to express their PICO requirements based on the assessment scope proposal and to submit additional PICO(s), if the assessment scope proposal does not 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.

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

During the scoping phase, inputs from patients, clinical experts and other relevant experts will be taken into account. According to recital 17 of the JCA IA-MP: *'These members should consult national authorities and stakeholders in accordance with the procedural rules of the respective Member State'*.

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

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 MP) or the intended use according to conformity assessment (in the case of MD and IVD MD) and their local healthcare situation. Relevant population(s) should be:

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

The definition of the relevant population(s) should be as specific as possible and avoid ambiguity. During the PICO survey and during the consolidation, 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. Therefore, MS should state in the wording of the patient population, the details of the target patient population. This definition of the MS is used throughout the scoping process and might be consolidated for the assessment process.

When appropriate, MS may define different subpopulations of the indication under assessment, according to MS needs. Subpopulations can be defined in order to address different policy questions. Potential reasons to define separate subpopulations, i.e. separate PICOs for each subpopulation, could be:

- different comparators are deemed appropriate for the different subpopulations,

- the therapeutic indication/intended use explicitly comprises different subpopulations, e.g. defined by certain tumor entities,
- the subpopulations have different prognoses and therefore different effectiveness is expected.

Intervention

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

Interventions for MP could comprise the application as monotherapy or combination therapy, as appropriate, also in addition to concomitant best-supportive care (BSC), or any background treatment. Typically, an assessment covers one intervention (a single MP or a single MD and IVD 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 might be a pharmacotherapy or a non-pharmaceutical intervention such as psychotherapy, radiation, physiotherapy, or surgery. On some 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, in collaboration with the MS concerned, 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. They could be requested by MS under ‘additional information’.

Key characteristics of the MD and IVD MD should be specified listing the device configurations/variants on the basis of information provided by the HTD. However, different versions of the MD and IVD MD could impact effectiveness and safety, and this should be considered.

Comparators

A comparator defines the treatment(s) against which the health technology under assessment should be compared. MS are expected to define the comparators to be used with each patient population they have requested. The word ‘treatment’ used in this guidance should be understood as referring to all health technologies.

For a given patient population, one or more comparators can be relevant for answering the policy questions of MS. Note that each comparator may be composed of one or more treatments (see below for details). Comparator treatments may or may not be licenced (for

MP: market authorisation, for MD and IVD MD: CE certificate) for the indication in the EU. A MS, according to its national context, could decide to include non-licensed treatments as comparators. The treatments comprising a comparator can be specific MP or MD or IVD MD but also drug classes, where appropriate. As there could be different practices across Europe regarding appropriate doses / regimens for each patient population in case of MP, the defined comparators should not contain information on dosage or regimen, but this will be considered by MS at a national level.

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.

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 MS should clarify whether a background therapy is part of the treatment in the group receiving the intervention and in the comparator.

Comparators and comprised treatments are not limited to pharmacotherapy or MD and IVD MD, but can also include any other intervention, for example psychotherapy, radiation, physiotherapy, surgery, diagnostic or prophylactic procedures or a combination of these. Comparators and comprised treatments can also include BSC or watchful waiting.

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 MS should clarify whether a background therapy is part of the treatment in the group receiving the intervention and in the comparator.

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

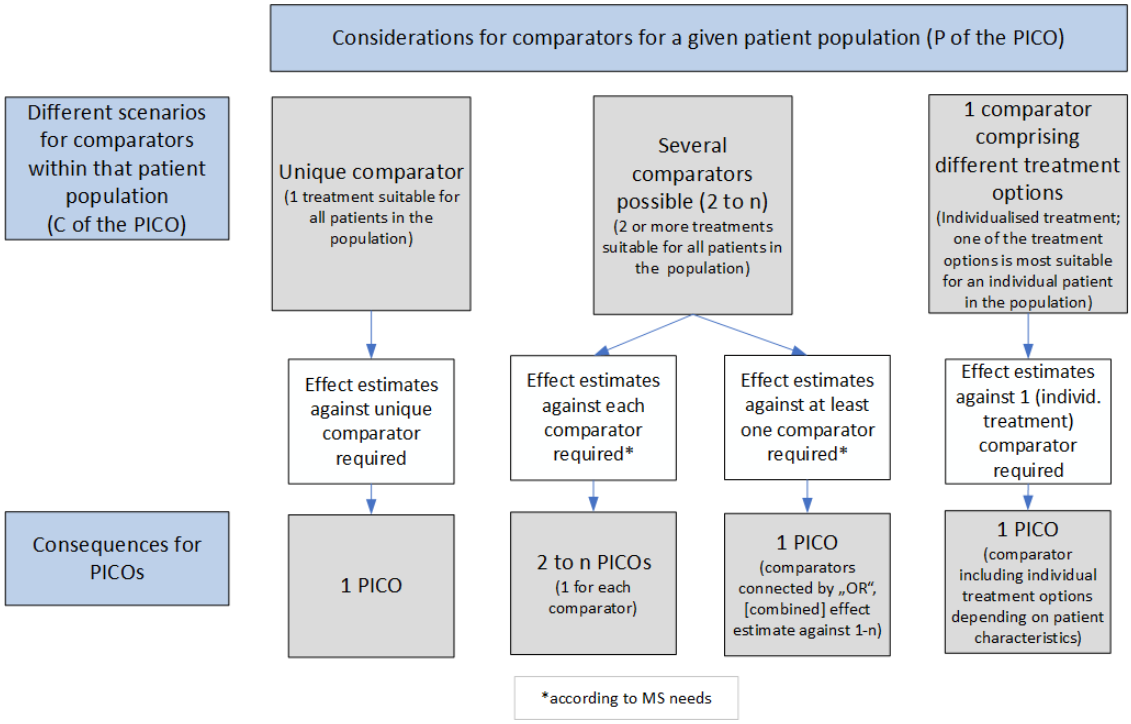


Figure 3: Considerations for comparators for a given patient population (P of the PICO)

Within a given patient population, different comparator scenarios can apply, with specific implications for the definition of PICOs.

If only one treatment which is suitable for all patients in a given population defines the comparator, a comparison (and thus effect estimates) against this single comparator is required. As shown in Figure 3, this situation is reflected in one PICO.

If several treatments, which are all suitable for all patients in a given population, are proposed, there can be two different situations:

1) A comparison (and thus, effect estimates) against each of these treatments is required. This results in each treatment being defined as a separate comparator.
2) A comparison (and thus, effect estimates) against at least one of these treatments is required. This results in the treatments being combined in one comparator.

In situation 1) a separate PICO is defined for each of these treatments (each defines the comparator of one PICO).

In situation 2) the different treatments are combined in one comparator (treatments will be connected by “OR“ to reflect the situation) and one PICO comprising this comparator will be defined. The effect estimates could be provided against one or more of the treatments comprising this comparator. If data for more than one of the treatments connected by “OR”

are available, an aggregated effect estimate should be provided, if methodologically appropriate. In addition, effect estimates should be provided for each of the included treatments individually.

MS may have different requirements with regard to the consolidation of PICOs with different lists of treatments in situation 2). This is explained and addressed in the description of the consolidation of PICOs below. MS should indicate in the case of an "OR" scenario whether they need to retain all comparator(s).

There might be situations in which a treatment 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, clinical guidelines often recommend a range of different treatment options. Actual treatments for individual patients are chosen based on patients' individual characteristics, e.g. pre-treatment, the severity of the disease or the general health status. To reflect this situation, the SoC is called "individualised treatment" and comprises the different treatment options recommended in the specific situation. This bundle of treatment options, the "individualised treatment", represents the comparator. One PICO against the individualised treatment comparator will be defined. In this scenario, a comparison (and thus one effect estimate [per outcome]) against the bundle of options summarised in 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 overall acceptability of data submitted on an individualised treatment comparator will be assessed at national level.

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 treatment options 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 by the MS when submitting their PICO(s).

Outcomes

Outcome is any concept that can be used for the estimation of relative effectiveness and safety of a health technology, such as mortality, remission, disease control, function, health-related quality of life (HRQoL), and symptoms.

MS will likely 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

Guidance on outcomes for JCAs[4]. Given that the JCA should not contain any value judgement or ranking of health outcomes, the listing of outcomes for the assessment scope should also be free of such judgement or ranking.

Additional information

MS can use this section to provide additional information for the assessor and co-assessor.

MS can use this section to request subgroup analyses to explore potential effect modifiers within the population (i.e., by defining subgroups (see definition in the glossary) e.g., age, sex, dose).

3.2 PICO consolidation

According to the IA JCA-MP Article 9(2): *"The HTA secretariat shall share the assessment scope proposal with the members of the JCA Subgroup. Based on the input received from the Member States, the assessor, with the assistance of the co-assessor, shall prepare a consolidated assessment scope proposal reflecting the Member States' needs"*.

Once the MS PICO(s) have been collected by the survey the assessor and co-assessor convert them into a set of PICO(s) that define the data requirements then conveyed to the HTD.

The objective of the consolidation is to ensure that MS needs are translated in the lowest possible number of PICOs (consolidated assessment scope proposal). One PICO comprises one population, one intervention (or combination), one comparator (which can include more than one treatment), and at least one outcome. The steps are explained below and are illustrated with an example.

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

To achieve the lowest possible number of PICO(s) during the consolidation phase, the assessor and co-assessor might contact the MS member of the SG to clarify open questions resulting from the PICO survey and discuss options for consolidation, especially if a specific PICO or a PICO component is only requested by one MS.

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 treatment(s) defining the comparator. The first row concerns the comparator scenario. It can be used to indicate whether comparison against the

4 Key documents – European Commission (europa.eu)

listed treatments are all required, or whether any one of those will suffice. The example is given for a MP. For MD and IVD, the 'full claimed indication' can be read as 'full approved intended use'.

Hypothetical example

This example is chosen to illustrate a combination of scenarios (Table 1 to Table 5).

Table 1: PICO of MS 1

Member State 1	
Population(s)	Full claimed indication
Comparator scenario (according to Figure 3)	Several comparators; effect estimates against at least one of them required
Comparator	Treatment 1, OR
	Treatment 2

Explanation: This MS expressed a requirement for the assessment regarding the full claimed indication only, and would require for this population either a comparison with treatment 1 or a comparison with treatment 2. This situation is described as "Several comparators (2 to n); effect estimates against at least one of them required" in Figure 3.

Table 2: PICOs of MS 2

Member State 2			
Population(s)	Full claimed indication	Subpopulation A	Subpopulation B
Comparator scenario (according to Figure 3)	Several comparators; effect estimates against at least one of them required	Several comparators; effect estimates against at least one of them required	Unique comparator
Comparator	Treatment 1, OR	Treatment 1, OR	
	Treatment 2, OR		
	Treatment 3	Treatment 3	Treatment 3

Explanation: This MS expressed a requirement for the assessment regarding the full claimed indication and subpopulations A and B. For the full claimed indication, the MS would require a comparison with either treatment 1 or treatment 2 or treatment 3. For subpopulation A, the MS would require a comparison with either treatment 1 or treatment 3. For Subpopulation B, a comparison with treatment 3 would be required. Subpopulation B reflects the scenario "Unique comparator" as shown in Figure 3.

Table 3: PICOs of MS 3

Member State 3		
Population(s)	Subpopulation A	Subpopulation B
Comparator scenario (according to Figure 3)	Several comparators; effect estimates against at least one of them required	Several comparators; effect estimates against at least one of them required
Comparator	Treatment 1, OR	
	Treatment 2	Treatment 2, OR
		Treatment 3

Explanation: This MS expressed a requirement for the assessment regarding subpopulation A and subpopulation B (and not the full claimed indication). For subpopulation A, the MS would require a comparison with either treatment 1 or treatment 2. For Subpopulation B, it would require a comparison with either treatment 2 or treatment 3.

Table 4: PICOs of MS 4

Member State 4		
Population(s)	Full claimed indication	Subpopulation B
Comparator scenario (according to Figure 3)	Several comparators; effect estimates against each of them required	Several comparators, effect estimates against at least one of them required; treatments cannot be dropped from the list during consolidation
Comparator	Treatment 3	Treatment 1, OR
	Treatment 4	Treatment 3

Explanation: This MS requires for the assessment regarding the full claimed indication a comparison with treatment 3 as well as a comparison with treatment 4. This situation is described as “Several comparators (2 to n); effect estimates against each of them required” in Figure 3. Regarding Subpopulation B, this MS would require a comparison either with treatment 1 or treatment 3, and has explicitly stated that these two treatments cannot be dropped from the list during the consolidation process (see below for further explanations).

Table 5: PICO of MS 5

Member State 5	
Population(s)	Full claimed indication
Comparator scenario (according to Figure 3)	One comparator comprising different treatment options (individualised treatment)
Comparator	Treatment 5 - Individualised treatment. The following treatment options are deemed appropriate: ▪ Treatment option 1 ▪ Treatment option 2 ▪ Treatment option 3 ▪ Treatment option 4

Explanation: This MS expressed a requirement for the assessment regarding the full claimed indication only, and for this population, requires a comparison against an individualised treatment, comprising 4 different treatment options.

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

The required population(s) should be set apart in separate tables and the columns of each table should list all MS that require this population. The first table has, by default, the full (expected) claimed indication as the population, if this population is requested by MS. The comparator scenario should be indicated in the row below the MS.

Example (based on Table 1 to Table 5)

Table 6: List of submitted treatments to be included in the comparators for the full indication (separated by Member State)

Full claimed indication			
Member State 1	Member State 2	Member State 4	Member State 5
Several comparators; effect estimates against at least one of them required	Several comparators; effect estimates against at least one of them required	Several comparators; effect estimates against each of them required	One comparator comprising different treatment options (individualised treatment)
Treatment 1, OR	Treatment 1, OR		
Treatment 2	Treatment 2, OR		
	Treatment 3	Treatment 3	
		Treatment 4	
			Treatment 5 - Individualised treatment

Table 7: List of submitted treatments to be included in the comparators for Subpopulation A (separated by Member State)

Subpopulation A	
Member State 2	Member State 3
Several comparators; effect estimates against at least one of them required	Several comparators; effect estimates against at least one of them required
Treatment 1, OR	Treatment 1, OR
	Treatment 2
Treatment 3	

Table 8: List of submitted treatments to be included in the comparators for Subpopulation B (separated by Member State)

Subpopulation B		
Member State 2	Member State 3	Member State 4
Unique comparator	Several comparators; effect estimates against at least one of them required	Several comparators, effect estimates against at least one of them required; treatments cannot be dropped from the list during consolidation
	Treatment 2, OR	Treatment 1, OR
Treatment 3	Treatment 3	Treatment 3

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

The goal of step 3 is to consolidate MS responses in the lowest number of comparators needed.

a. Unique treatment: If a MS requires a unique treatment for a given population, it is selected. This is done for all MS. Every different treatment is assigned a separate PICO and therefore defines the comparator of a given PICO.

b. Several comparators, effect estimates against each of them required: for every required treatment, a separate PICO is assigned, with each treatment defining the comparator of each PICO.

c. Several comparators; effect estimates against at least one of them required: in this situation MS requirements may result in different approaches to consolidation.

    1. MS indicate during the PICO survey that treatment(s) may be dropped during consolidation:

       In this case the following steps for PICO consolidation are possible:

       - If at least one of these required comparators is already included for the respective population after step 3a and 3b of the consolidation, all other required comparators may be dropped.

       - If this is not the case, the list of treatments is crosschecked against all remaining PICOs with treatment lists (for a given population). The lowest number of treatments needed to satisfy the requirements of MS will determine which treatments will be selected. If no preference can be given, this will be highlighted. In this case, the comparator definition will include the alternative treatments. Again, a separate PICO for every additional comparator scenario (in this case with alternative treatments) is assigned.

    2. MS indicate during the PICO survey that all treatment(s) need to be retained during the consolidation:

- In this case the full list of treatments must be retained.
- Consolidation of PICOs is only possible, if other MS require the exact same list of treatments.

To allow for consideration of MS requirements the need to retain all treatments in the OR scenario must be included in the PICO survey.

d. Individualised treatment: one comparator comprising different treatment options: If several individualised treatment comparators are requested by MS, a discussion between assessor, co-assessor and MS should explore the opportunity to adjust the components of the individualised treatment to consolidate the individualised treatment options. However, this process should always consider the needs of all MS. If individualised treatment options differ, different PICO(s) might have to be formulated.

Example

Subpopulation B

Step a: One unique comparator

Only MS 2 requires a unique comparator for a particular population; which is treatment 3 for subpopulation B. This results in one PICO.

Step b: Not relevant

Step c: Several comparators; effect estimates against at least one of them is required

Considering MS 3 has not explicitly stated that treatments cannot be dropped from its list during consolidation, the needs of MS 3 with regard to subpopulation B are also fulfilled with the selection of treatment 3. Therefore, a PICO with treatment 2 is not necessary and will not be included. However, considering MS 4 has explicitly stated that treatments cannot be dropped from its list during consolidation, an additional PICO with the comparator "treatment 1 OR treatment 3" must be constructed for subpopulation B.

Step d: Not relevant

Full claimed indication

Step a: Not relevant

Step b: Several comparators; effect estimates against each of them required

MS 4 applies the *"several comparators; effect estimates against each of them required"*-scenario and requires two treatments (3 and 4 are both required). This results in two PICOs.

Step c: Several comparators; effect estimates against at least one of them is required

MS 2 applies the *"several comparators; effect estimates against at least one of them required"*-scenario and requests any of treatments 1 or 2 or 3. Hence, with the selection of treatment 3 to fulfil the needs of MS 4, the needs of MS 2 are also fulfilled. However, with the selection of treatments 3 and 4, the needs of MS 1 are not fulfilled because this MS needs treatment 1 or 2. Therefore, an additional PICO with the comparator "treatment 1 or treatment 2" is constructed.

Step d: Individualised treatment

MS 5 requires a comparison against an individualised treatment. As a consolidation of an individualised treatment scenario with a "several treatments" scenario is not possible, a separate PICO is constructed to fulfil the needs of MS 5.

Therefore, in total, this population requires at least four PICOs: two PICOs that cover the needs for MS 4 (treatments 3 and 4) and one PICO that covers the needs of MS 1 and one PICO that covers the needs of MS 5. The needs for MS 2 are included in those PICOs.

Subpopulation A

Step a: Not relevant

Step b: Not relevant

Step c: Several comparators; effect estimates against at least one of them required

With treatment 1, the requirements of both MS 2 and 3 can be satisfied by one PICO, if they agree with the consolidation. In this situation, treatment 2 and treatment 3 are omitted during the consolidation process, unless one of the MS objects.

Step d: Not relevant

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

1) Each PICO is placed in a separate column. The defined comparators are placed in the row below.
2) The required outcomes are added in the row below the comparators. For this, the guidance on outcomes for JCA should be followed[5]. In principle, all outcomes should be included for all PICOs (see Table 9).

Figure 4 summarises the four steps of the PICO consolidation process. Applying these four steps should result in the lowest possible number of PICOs that meet the needs of MS. After

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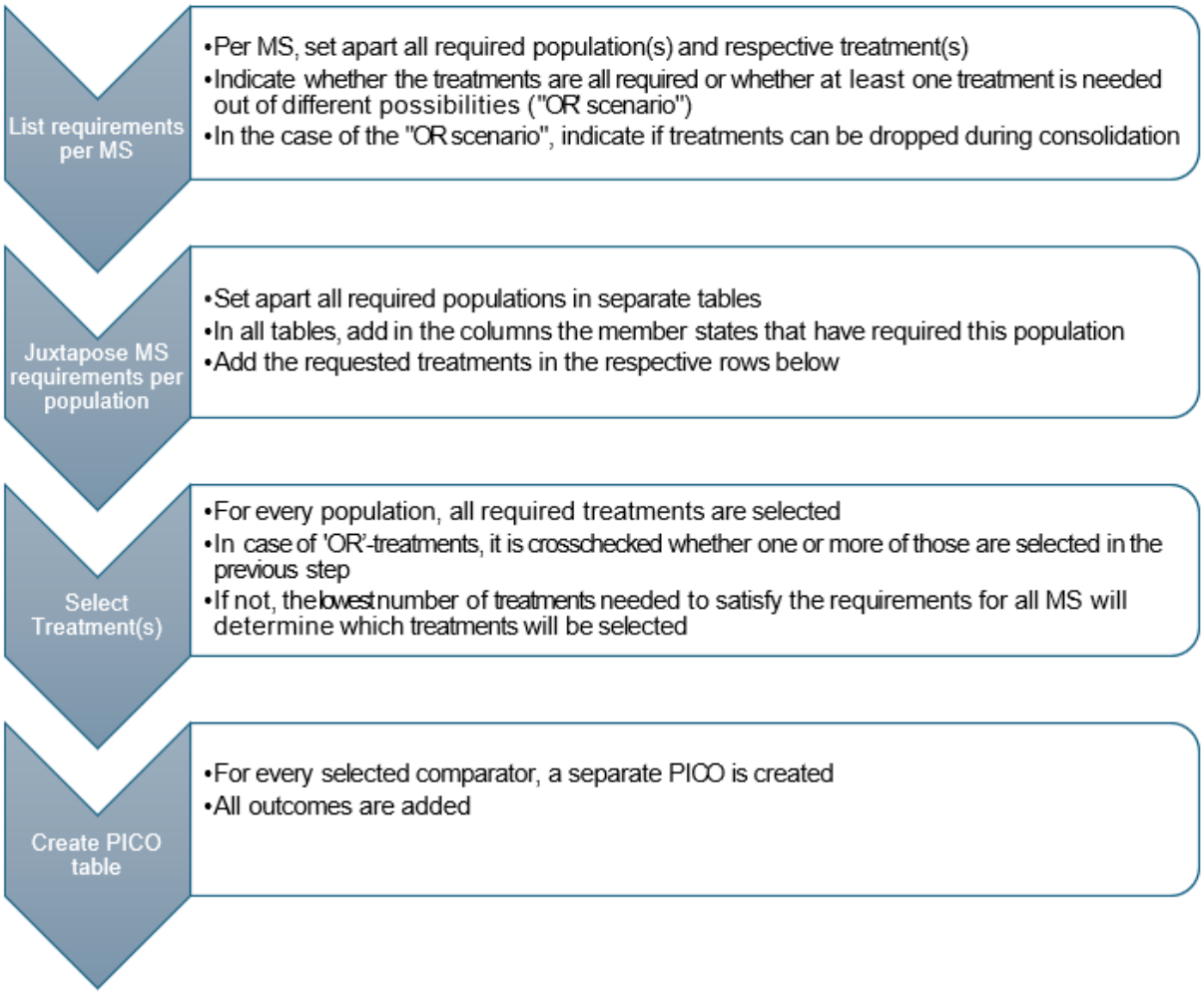
applying these four steps, whether the needs of MS are indeed met should be checked by the MS. The assessor and co-assessor will share the consolidated assessment scope proposal with the member of the SG asking MS for confirmation that their needs were met or if they require adaptations. Such confirmation finalises the PICO consolidation. The whole process should be transparent and accessible for all SG MS. The PICO table is the outcome of the PICO consolidation and can be used for further reference in the scoping and assessment process.



MS: Member State; PICO: population, intervention, comparator, outcomes

Figure 4: The four steps of the PICO consolidation process

Example (based on Tables 1–8)

Table 9: Consolidated PICOs based on Member State requests

	PICO 1	**PICO 2**	**PICO 3**	**PICO 4**	**PICO 5**	**PICO 6**	**PICO 7**
P	Full claimed indication	Full claimed indication	Full claimed indication	Full claimed indication	Subpopula-tion A	Subpopula-tion B	Subpopula-tion B
C	Treatment 1 OR Treatment 2	Treatment 3	Treatment 4	Treatment 5 - Individualised treatment	Treatment 1	Treatment 3	Treatment 1 OR Treatment 3
O	All outcomes	All outcomes	All outcomes	All outcomes	All outcomes	All outcomes	All outcomes

All consolidated outcomes submitted by MS during the PICO survey are listed for all consolidated PICOs. Outcomes may be consolidated by merging variations in wording of the same outcome without content-related implications, if the respective member states who requested the outcome agree.

3.3 Assessment scope finalisation

According to IA JCA-MP Article 9(3): *'The HTA secretariat shall share the consolidated assessment scope proposal with the patients, clinical experts and other relevant experts selected in accordance with Article 6 and give them the opportunity to provide input*'.

According to IA JCA-MP Article 10(1): *'The JCA Subgroup shall discuss the consolidated assessment scope proposal referred to in Article 9(2), as well as the input of patients, clinical experts and other relevant experts during an assessment scope consolidation meeting. The JCA Subgroup, via the HTA secretariat, may invite patients, clinical experts and other relevant experts to provide their input during a dedicated part of the assessment scope consolidation meeting'*.

The JCA SG finalises the assessment scope during the assessment scope consolidation meeting, by consensus as it will respect MS requirements.

3.4 Changes to the therapeutic indication

Given the timelines of the JCA, for MP, the scoping process has to be completed before Committee for Medicinal Products for Human Use (CHMP) opinion. This means that the anticipated population might change after the JCA assessment scope has been defined because of changes introduced by the regulatory process.

The IA JCA-MP specifies in Article 16 the process for a change to the therapeutic indication.

4 Information to the HTD

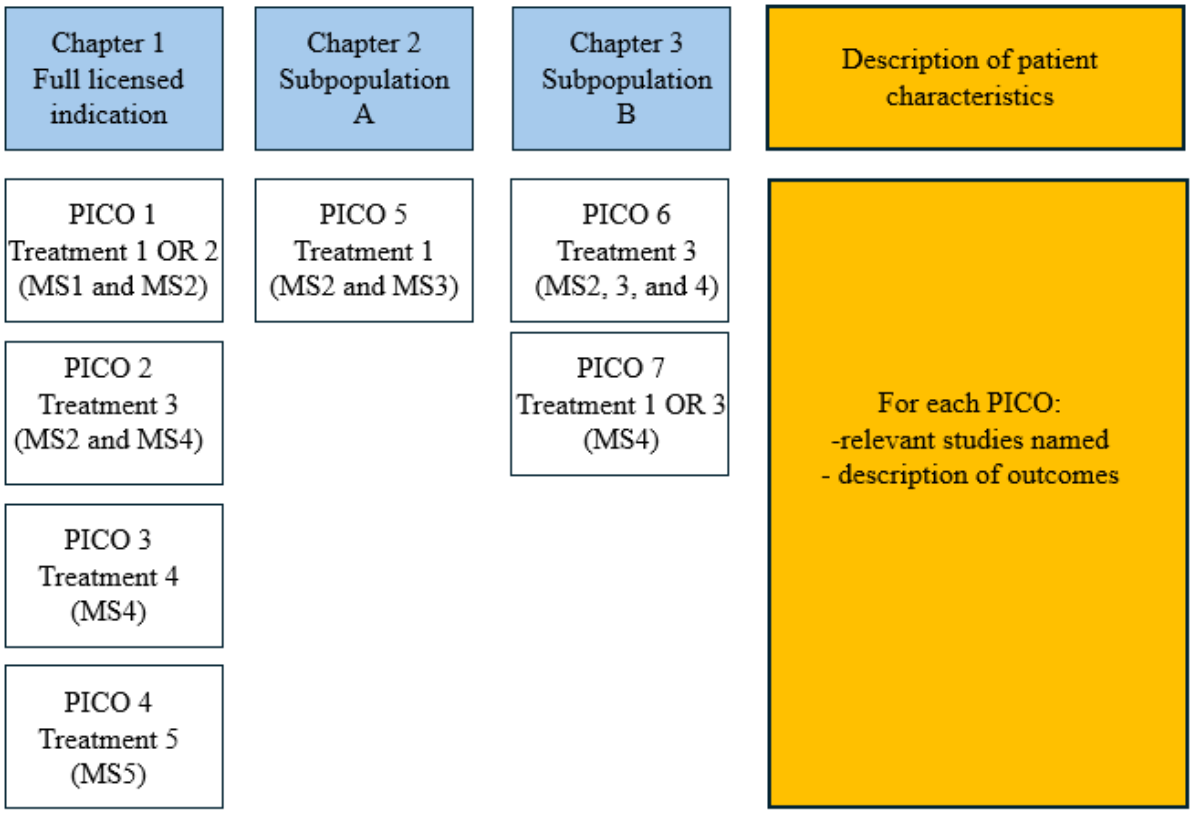
IA JCA-MP Article 10(3): *'The HTA secretariat shall share the assessment scope finalised by the JCA Subgroup with the health technology developer in the Commission's first request referred to in Article 10(1) of Regulation (EU) 2021/2282'*.

IA JCA-MP Article 11: *'Upon request of the health technology developer, the HTA secretariat shall invite the health technology developer to an assessment scope explanation meeting with the JCA Subgroup. The meeting shall take place no later than 20 days from the day on which the JCA Subgroup finalises the assessment scope'*.

5 Data presentation in the JCA report considering the PICO(s)

Since the assessment scope is mostly considered to be policy driven, it may contain PICOs for which no evidence is available. However, in this case, the JCA report will identify evidence gaps with regard to decision making in health care systems. HTDs will have to justify and provide a rationale when no data for a specific PICO are submitted. The appropriateness of the provided rationale will be assessed by the assessor and co-assessor and the overall acceptability will be decided at national level. If a study (or a dataset) is considered to be able to address (even partially) several PICOs, duplication should be avoided throughout the JCA.

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 report comprises different chapters of assessments structured by population. Figure 5 illustrates the structure of data presentation for the example developed in section 3.2.



MS: Member State; PICO: Population, Intervention, Comparator(s), Outcomes.

Figure 5: Example of data presentation according to PICO(s)

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 5 of this guidance, the report will constitute the following three assessment chapters: Full licensed indication (MP) or full approved intended use (MD and IVD MD); Subpopulation A; and Subpopulation B. Note that only the first chapter has four subsections because it encloses four different comparators (1: Treatment 1 OR 2, 2: Treatment 3, 3: Treatment 4, and 4: Treatment 5). In Chapter 3 of the example, Treatment 3 is used once again as a comparator; 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 are informed by the same studies. 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 (Annex I, HTAR). In addition, the intervention is common 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 HTAR and IA JCA-MP and IA JCA-MD templates.

6 Reporting of original statistical analyses versus PICO driven analyses

As described above, the PICOs are developed based on the national policy questions to be answered by the assessment. In many cases, the studies available for the JCA might cover one or more 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 re-analysed 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 JCA by the definition of the PICO. Any such deviations should be clearly mentioned by the HTD in the submission dossier. The re-analyses will be provided by the HTD in the submission dossier.

In the JCA report, it should be clear which data sets are from an analysis according to the original study planning (i.e., analyses according to the original protocol and statistical analysis plan of the study without regards to the PICO questions) and which are based on re-analyses resulting from PICO requests. In any case, the original study analyses will be included in the dossier.