EUnetHTA 21 response to the public consultation comments on the draft practical guideline 4.2 Scoping Process

EUnetHTA 21 wishes to thank the many organizations and individuals who have responded to the public consultation of this practical guideline. We have taken all comments into consideration. Due to the large number of comments received, we answer the comments on an aggregated basis. Textual suggestions have been taken into account but are not justified here.
The comments are aggregated into general themes. Specific elements herein are preceded by a hyphen. The EUnetHTA 21 responses are found below each (group of) comment(s). For abbreviations, we refer to the guideline.

Comments regarding the process:

- The process should be detailed more regarding the timelines, clock stops, details for MD are lacking
- The timelines are too limited for HTD's to prepare a dossier and for MS to respond to the PICO survey
- Potential discrepancies between EUnetHTA 21 and the process under the HTAR
- In which situations can the PICO be changed after being finalized
- Label changes during the EMA-procedures require a separate process, and the cooperation between regulators and assessors should be in place to prevent this

In its final version, this practical guideline only contains the unique timeline stated in the HTAR relevant for the scoping process of medicinal products: D-45 prior to the envisaged date of the opinion of the CHMP (Article 10(1)). This is the latest possible deadline for submission by HTD after a first request.
Other exact schedule and timeframes (e.g. starting point for scoping process, communication of PICOs to HTD) or related procedure (for example, possibility or not for clock stop) are not clearly stated in the HTAR, and cannot be defined in this guideline only without considering the overall process.
Timeline for national procedure is out of scope of this guideline, which is only dedicated to European level.
The timing of the PICO survey included in the flow chart in the guidance only covers the time in which the survey can be filled in. MS will have time before this time slot to define their PICO(s).
A change in the finalized PICO might be necessary if a situation arises where any of the PICO-elements change from the assumptions used at the time of scoping. These are not limitatively described. An example may that the assumed label changes during the EMA process. Regarding this specific situation, a label change during the EMA process is, on the basis of experience in national assessments, assumed to be relatively infrequent (10% of the cases). Presently, no solution can be given as to how a cooperation between EMA/MD-Regulators and HTA can be designed within the framework of the HTA Regulation in order to include labelling changes in the assessment process at an early stage. Also given the strict timelines in the HTA-R, this issue could not be resolved in the context of EUnetHTA 21 and therefore a recommendation for the future has been made (see paragraph 3.4). This will partly be addressed in an implementing act (interaction with EMA).

Comments regarding the role of the HTD in the scoping process:

- A PICO should be proposed by the HTD or part of the consolidated PICO
- A PICO should be proposed by the lead assessors of the JCA
- HTD should indicate data availability
- HTD should be involved and/or consulted in consolidating and/or validation of the PICO

We received divergent comments on the involvement of the HTD. Some were supportive of our proposal, and others (the ones answered here) in favour of including HTD with a proposed PICO or an involvement in the consolidation process.
Based on the HTA-R, we have developed the guideline based on an inclusive assessment scope which reflects Member States' needs in terms of parameters and of the information,

data and other evidence to be submitted by the health technology developer (Article 8(6)). This means that the assessment scope is Member State driven and not dependent on data availability. We therefore put forward that the HTD does not submit any PICO and should not be involved in the PICO consolidation process. Also, the assessor of the JCA should not put forward a PICO for the PICO survey.
In EUnetHTA 21, HTD input is required via a letter of intent, as there is no formal exchange of information with EMA. The same will apply for MD as there is no other way to inform the assessor and co-assessor about the intended use.
Under the HTAR, the HTD input required for the PICO survey, i.e., the intervention under assessment and the claimed indication can be provided by EMA /MD regulators. In the HTAR context, we believe that a systematic meeting with HTD after PICO consolidation would not be feasible and could have negative consequences on the assessment process. Regular feedback from such a scoping meeting to the MS as well as further feedback from the MS to the Coordination Group on how the meeting possibly changed the national PICO would be required, and this would not be possible in terms of time and human resources. We will nevertheless test feasibility of a meeting in EUnetHTA21 (see below).

- There should be a scoping meeting with the HTD

To further evaluate the feasibility and usefulness we plan, as a pilot within the context of EUnetHTA 21, to hold an informational meeting with HTD. This will be explained in deliverable 7.1. The benefit of this exchange will be evaluated at the end of the EUnetHTA 21 productions.

Comments regarding the rights and obligations of the HTD

- Which information does the HTD have to supply for the scoping process
- Per HTA-R, the HTD should not be restricted to supply any information
- Is the HTD responsible for initiating the process

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 through in a letter of intent (LoI) submitted by the HTD, to the EUnetHTA 21 secretariat and this information will be made available to the MS. The process under the HTAR has to be developed.

- The HTD should be asked to include information on ongoing clinical trials

As the PICO questions should not be data driven but should reflect MS policy questions, information on finalized or ongoing studies is not relevant at this point of the process.

- The HTD should have insight in the results from the PICO survey and from the validation process

It is unclear why an insight in the individual MS PICOs would be required. As the Regulation stipulates that MS needs should be met and this is ensured by the consolidation process and validation by the MS in the Coordination Group, the information on individual MS PICOs does not have any further positive impact to the JCA process and will therefore not be provided.

- What are the consequences if the HTD fails to meet the requested scope
- The HTD does not have to meet the full requested scope
- The secretariat should ensure that the information provided by the HTD is comprehensive and adheres to the requested scope

We consider the (claimed) right of the HTD not adhering to the requested PICOs and consequences thereof are out of scope for this guideline. These processes, including the

verification of the completeness of the submission dossier, are under development and will be described elsewhere.

Comments regarding the rights and obligations of the Member States

- MS should include a rationale for their inputs to the PICO survey

In the PICO survey, a rationale for the specific PICO is not requested from the MS. In principle, the rationale for a MS PICO is the research question coming from their health care system. One example would be that relevant comparators are based on the treatment available in a MS. However, the JCA CSCQ meeting offers the opportunity for assessors and co-assessors to clarify open questions.

- MS requested PICO should be mandatory for further national implementation process

Mandatory use of the PICO that a MS provides in the PICO survey is not a (legal) requirement from the HTA-R. The discussion on the national process is out of the scope of the HTAR and this guideline. It is up to the MS to decide how their input into the scoping process will affect their processes on the national level.

- What is the consequence of a MS not answering to the PICO survey in time

PICOs not submitted (in time) cannot be taken into account in the consolidation process. The specification of a minimum number of MS with responses does not seem necessary, as participation by most MS is expected. Consequences of MS not participating in the PICO survey on any national procedures are out of the scope of this guidance.

Comments regarding the (potential) PICOs resulting from the process

- There should be one (European) PICO resulting from the scoping process. Other requests from MS should be dealt with on the national level
- In the current description of the process, the number of resulting PICOs will potentially become unfeasibly large

We wish to emphasize our previous answer that, based on the HTA-R (article 8(6)), the assessment scope should be inclusive and should therefore reflect Member States' needs. This means that the assessment scope is Member State driven and not dependent on data availability. Therefore, there is no formal limitation to only one PICO, and more than one could be requested,
We do not expect a situation in which the scope of a JCA comprises a very large number of PICOs. Typically, only a few different treatment standards across Europe exist (comparators). Some differences may occur due to different approaches of health care systems to the patients to be treated (populations). Which of these differences becomes relevant for any individual new technology to be assessed depends on the disease area or the current treatment landscape.
Thus, we expect larger groups of MS using the JCA of a given PICO question to inform decision making in their health care systems. This constitutes a significant efficiency gain.
In case a specific PICO would only be relevant for 1 MS, the consolidation procedure already includes contact and discussion with the MS concerned to achieve the fewest number of PICO questions possible. A new step introduced into the process is the explicit discussion of cases of PICO questions affecting only 1 MS in the validation meeting of the assessment scope. This will be an additional opportunity to clarify whether a certain information requirement might be covered at a national level or can be considered to be scientifically covered by other PICO(s). The guidance is updated accordingly. We will also add a statement that the example given for the consolidation process is A. hypothetical, to fully examine most, if not all, possibilities that may occur and to explain the consolidation process; and B. in practice not expected as a rule to be that complex within one JCA.

- Multiple PICO's may lead to adaptations of the original statistical analysis plan, which may in turn lead to uncertainties stemming from (post hoc) analyses of the primary studies (and what are acceptance criteria for post hoc analyses) and may lead to multiplicity issues. Should indirect comparisons be performed (and how). And other questions regarding specifications of analyses

The available studies may need to be reanalysed or evaluated for suitability to the assessment scope. For example, it could be that the original study population is broader than that

described in a certain PICO. The types of analysis, the analysis of the degree of certainty, and multiplicity issues are out of scope of this guideline. There are a number of methodological guidelines that will provide details on this topic (D4.5 and D4.6 and the JCA template notably; please see Article 9(1)). It is not necessary that the original study analyses are described in detail in the dossier if they do not cover a PICO, but they have to be submitted for completeness and transparency (according to the regulation CSRs have to be submitted).

- PICO selection should be based on consensus instead of qualified majority

The PICO has to meet the MS needs. Therefore, it may be possible for the JCA to address multiple PICOs. To obtain the lowest number of PICOs, not all optional PICOs have to be assessed. This is ensured by the consolidation process. The guideline describes that a discussion of open questions from the PICO survey. A decision based on consensus should be therefore possible.

Comments regarding the role of patients, and clinical and other relevant experts:

- There should be more involvement of national patients and experts
- There should be more involvement of EU patients and experts
- There should be criteria on the involvement of patients and experts
- Independent expert groups/statisticians should be included as well
- It is unclear how patients and experts are informed and how they can cooperate in the process
- How is the input from patients and clinical experts taken into account

We believe that the input from patients and clinical experts is of high value for the scoping process. Moreover, their input (on the EU level) is a requirement per HTA-R. Many specific aspects on patients, health care professionals and stakeholder involvement will be described in a specific guideline. Therefore, we consider the details of their involvement out of scope for the scoping process guideline. Alignment between the development teams of those different deliverables have taken place in order to ensure that all relevant aspects will be considered in any of those deliverables, and that duplication is avoided.
We have made changes in the guideline to better specify the involvement of patients and clinical experts in the scoping process. In order to be able to incorporate the EU input, we made an amendment to have EU level patient and clinical expert inputs included before the survey. MS can as a consequence incorporate these inputs in the development of their scope. The involvement of experts and patients to the national PICO has to be realized on MS level, but is not enforceable on the basis of the HTA-R. For MS that have not established a national process to involve clinical experts and patients, the corresponding European statements are available.

- What is the definition or position of 'other relevant experts'

We clarified in the text that this concerns statisticians or methodological experts.

- The scoping guideline should ensure that the experts are validated and published transparently

This will be described in a dedicated guideline on the involvement of experts. There will also be a guideline on the handling of (potential) conflict of interests.

Comments regarding the parameters defined in the PICO's

- The comparators studied in the trials should be included in the assessment scope
- Comparators should have market authorization for the population under assessment
- There should be a medical rationale (e.g., mentioned in (EU or national) guidelines or studied in trials) for a comparator to be included in the assessment scope
- Comparators based on non-comparative evidence should be accepted

- MS should be able to express alternative comparators
- The 'OR'-description for optional comparators during the scoping process may lead to the exclusion of the comparator in the trial.

We do wish to emphasize our previous answer that, based on the HTA-R (article 8), the assessment scope should be inclusive and should therefore reflect Member States' needs. This means that the assessment scope is Member State driven and is not dependent on data availability. As a consequence, we do not pose any further requirements (such as medical rationale of the comparator or the study design in which they have been studied) on the comparators that can be used in the PICO's resulting from the scoping process. This also means we do not add by default studied comparators in the scope, nor do we exclude off-label comparators.
According to the experience, MS will list the most relevant comparators according to their policy question. It is rather unlikely that the most relevant, evidence based, comparator is listed by one MS only and therefore will not be part of the final PICOs. However, to obtain the lowest number of PICOs, not all optional PICOs may be selected as a consequence of the consolidation process. The PICO consolidation process plans a discussion of open questions from the PICO survey, which is aimed to resolve any exceptional circumstances or outcomes of the PICO survey and consolidation. A situation where, due to the response of a single MS, a relevant (optional) comparator is excluded, might be resolved through this process.

- The Intervention and Population should follow the SPC
- The guideline should state clear criteria for inclusion of a specific background therapy as part of the intervention

The population of the SPC is the starting point of the PICO survey. However, MS are free to define their Intervention and Population, according to their national needs. Background therapy varies from case to case and cannot be described in a generic, abstract general guideline for all case types in more detail than currently is done in the guideline (please see 3.1.4). However, describing whether a background therapy is part of an intervention (and/or comparator) has to be stated in the PICO.

- Outcomes should be provided separately from the PICO
- If a MS requests different outcomes, should those be combined and be part of every PICO

Outcomes are inseparable from the PICO. In practice, we expect that outcomes are similar across PICOs within each patient population. All outcomes should in principle be included for all PICOs (please see 3.2.4).

- When the scoping results in multiple comparators in the "OR"-situation, without a preference for one or another, does the HTD have the liberty to choose which comparator is used in the submission?

Yes, this is indeed the case. It is described in step 3 of the consolidation process (3.2.3).

Comments regarding alignment of PICOs

- PICO's with similar populations but different comparators should be combined in 1 PICO with different comparators
- PICOs for similar active substances should be aligned across indications

A new PICO is defined if different comparators or populations have to be addressed. PICOs aren't by definition constant over time, so the scoping process is needed to identify changes in the research question, for example, due to change in the treatment landscape.

Comments regarding the PICO survey

- Who is responsible for responding to the PICO survey at the MS level
- MS should take national policies into account when responding to the PICO survey

- Dosage is part of intervention instead of additional information

Which organisation(s) will provide input for the PICO survey is decided at the national level. Whether or not this information will be published is out of scope of this guidance. Any national policies beyond those resulting in the PICO (e.g. specific regulations concerning the reimbursement and pricing of ATMPs, orphan drugs etc.) will have to be considered at national level. The JCA is aiming at providing information on the relative clinical effectiveness and safety of a new treatment. The consideration of this information is decided at the national level.
The paragraph of the guidance regarding dosage is referring to dose as a potential effect modifier. This is different from the general definition of the intervention which will be based on the intervention characteristics such as the submitted and/or approved dose range.

- How is 'other evidence', next to the PICO components, being handled

According to the current experience with JCAs additional requests beyond the PICO are uncommon. Therefore, the current guidance plans to discuss specific requests for additional information (beyond potential effect modifiers or specification of background therapy which is covered by the guidance) on a case-by-case basis. Based on this experience the guidance might be amended to cover any upcoming aspects.

- The objective of the PICO survey should not include the MS needs in terms of analysis, as is stated in the guideline. The PICO survey should be limited to input on the research question and data requirements.

This reflects a requirement from the regulation. Therefore, we have not made any changes to the objective.

- Which platform will be used for the PICO survey and how can confidentiality be guaranteed

We consider this a technical elaboration which does not need to be detailed in this practical guideline. We do emphasize that, naturally, all actions need to comply with GDPR.

Comments regarding the role of previous Joint Scientific Consultations

- All PICO's from JSC should be included in the assessment scope
- Assessors need to be aware of any previous JSC
- HTD should be enabled to provide information about what was done with JSC input from MS
- Are MS bound to input from JSC

The regulation stipulates that the JSC "shall not give rise to any legal effects on MS, the Coordination Group or the HTD" and "shall not prejudice the JCA". Therefore, in principle, the assessment scope is not limited by the JSC. As stated in the guideline, the MS will be made aware of any JSC that might have taken place for the medicinal product or MD under discussion. 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.

- Scoping should take place at the JSC level and not JCA, updated at JCA level only if needed

The scoping process during JCA is clearly stated in the HTAR (Article 8), and JSC are optional.

- The HTD should be informed when any changes occur that would lead to a different PICO than discussed in JSC

HTDs will be informed about the PICO(s) after validation. This is the earliest point at which the information on the PICO is final.

- Regulatory scientific advices should be kept confidential and only be disclosed after consent from the HTD

Information on JSC during the process will be provided according to the requirements of the Regulation. We would like to point out that according to Annex I and II of the Regulation the HTD is required to provide an explanation on any deviation from the JSC in the submission dossier.

Comments regarding MD's and IVD's

- For MD, the PICO may be unknown at the time of scoping, because MS do not always immediately assess MD

Regarding MD, the assessment including all process steps (like scoping process) is required by the HTAR and is initiated by the CG. Assessment reflects the current state of knowledge/affairs.

- The population may be narrower than the intended use from the conformity assessment

This is foreseen in the guideline. MS can request subpopulations in the PICO survey.

- Specific information regarding IVD's are lacking

Information on the regulatory procedure for medical devices and IVD is not yet as differentiated as for pharmaceuticals. But IVDs can - where applicable - be added in the future.

Miscellaneous comments

- Vaccines and national immunization processes merit separate notice

We see this as an exceptional circumstance. Whether or not any separate process is needed can currently not be established. We recommend this for future consideration.

- A definition of scoping should be provided

We believe that the 'assessment scope' and the process in which it is formed is adequately described in the guideline.

- Methodological/technical/statistical concepts should be introduced and/or explained, and specifications for analysis should be provided

The objective of the guideline is to define a process in which the assessment scope is established. The resulting PICOs in turn specify the data required from HTD. It is expected from the HTD to analyse the data in such a way that it fits the PICOs. See other methodological guidelines (under development) for details on methodology. The presentation of data / analyses will be introduced in the submission dossier. These topics are out of scope for this guideline.

- The data presentation should be covered in deliverable 5.1 and 5.2 instead of this guideline
- The templates should be an appendix to this guideline, since they are expected to describe data presentation and the expectations from HTD's

According to the project plan of this deliverable, the Impact of the PICO on data presentation and the HTA report has to be addressed. However, the details are covered by (independently published) deliverables D5.1 and D5.2

- Does the degree of deviation from the original SAP and protocol needs to be assessed

No, an assessment of the degree of deviation is not necessary. It has to be made transparent which analyses were pre-specified and which were performed post-hoc, and which method was used. See also guideline D4.5 (Applicability of evidence).

Name organisation & abbreviation	Country
EFPIA (European Federation of Pharmaceutical Industries and Associations)	Belgium
EURORIDS	Belgium
European Union of General Practitioners/Family Physicians UEMO	Belgium
BIOTRONIK SE & Co. KG	Germany
Ecker + Ecker GmbH (E+E)	Germany
SKC Beratungsgesellschaft mbH (SKC)	Germany
Verband Forschender Arzneimittelhersteller (vfa) e.V	Germany
GKV-Spitzenverband, GKV-SV	Germany
German Medicines Manufacturer´s Association (BAH)	Germany
Finnish medicines agency, Fimea	Finland
Bundesarbeitsgemeinschaft Selbsthilfe von Menschen mit Behinderung und chronischer Erkrankung und ihren Angehörigen e.V. (BAG SELBSTHILFE)	Germany
European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)	Belgium
Edwards Lifesciences	Europe
GSK	UK
IGES Institut GmbH and HealthEcon AG	Germany
F. Hoffmann-La Roche Ltd (Roche)	Switzerland
Lumanity	Lumanity is a global company with several European entities, including in Ireland and the Netherlands.

Advanced Medical Services GmbH - AMS	Germany
Medtronic	Switzerland
AstraZeneca (AZ)	Global (UK based)
European Federation of Statisticians in the Pharmaceutical Industry (EFSPI) HTA SIG	Europe
Vaccines Europe	Belgium
Norwegian Institute of Public Health (NIPH)	Norway
Alliance for Regenerative Medicine (ARM)	Belgium
AIM – International Association of Mutual Benefit Societies	Belgium
Takeda Pharmaceuticals International AG	Public affairs office in Belgium, European head office in Switzerland, pan-European local operating companies
MedTech Europe (MTE)	Europe - Belgium

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Mihai Rotaru EFPIA	General		As a general comment, we wish to highlight three related matters regarding the proposed scoping process that EFPIA believes requires further consideration, leaving them unresolved may result in the objectives of the HTAR not being met. 1. **Sufficient time for HTD to produce a high-quality dossier**: A survey of our membership found that companies require between 4 to 5 months to prepare a dossier for submission. This is consistent with the experience of those companies that participated in the JA3 REA pilots. Importantly, the time required to produce the submission will be sensitive to the complexity of analyses that flow from the agreed set of PICOs – the greater the complexity and scope, the more time will be required. Indeed, the scoping process most likely needs to commence earlier than currently envisaged so that the requirement of a final JCA report being made available as per the HTAR can be met. It is recommended that for each of the key process steps under consideration (e.g. Scoping and PICO development), that they be presented within the context of the timeline of the complete JCA process. This will provide stakeholders with an overview of the time-sensitive deliverables and a better appreciation of the feasibility of meeting each step in the process. **2. Breadth of the Scope for EU JCA** It is critical that the scoping and PICO development process enable an EU JCA that meets both the needs of the Member States (MS) and the development of a dossier that is sufficiently focused to inform the final high-quality assessment. The proposed methodology for the PICO development risks, for some products, introducing unnecessary analytical complexity as well as corresponding evidentiary uncertainty. This is especially the case where local and historical variations in clinical practice that exist across the MS translate into a multiplicity of requests for analyses of country specific sub-populations that are not pre-specified in the trial data and for the use of a multitude of comparators that require the adoption of indirect treatment comparisons – the	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			methods for which are not looked upon favorably by all EUnetHTA21 members. Whilst the HTAR states that the scope should be inclusive and address all MS' needs in terms of data and analyses (Recital 25; Art. 8.6), it is also clear that this does not mean all possible patient groups and all comparators required by MS should be included in the EU JCA scope. The HTAR is also clear that MS can conduct complementary clinical analyses to ensure that the needs and characteristics of individual health systems are accounted for, including different patient groups or comparators, (Recital 15). EFPIA recommends that the JCA adopt an explicitly European perspective and focus on that which is common to Member State health systems rather than aiming to meet all the needs of each. The HTAR allows for what material differences that do exist between MS to be accommodated in subsequent local, complementary clinical analyses. **3. Manufacturer/Health Technology Developer (HTD) involvement in the scoping and PICO development process** Taking into account *both* the need to develop and align on a scope/PICO for the JCA, *and* to ensure sufficient time for a HTD to develop a high-quality dossier to support a JCA that is informative to what is *common* to all Member State health systems, we would like to suggest some adjustments to the proposed PICO development process. Our recommendations include involvement of the HTD in the process, which we believe will make the PICO development process more efficient and allow the HTD to commence preparation of the dossier earlier. Proposed PICO development process: **Step 1**: the HTD submits a **letter of notification** to the Coordination Group, following acceptance of the EMA dossier, outlining the characteristics of the technology as well as the intended PICO(s) for the assessment. Similar to the EUnetHTA JA3pilots, the HTD should propose a base-case European PICO, based on the expected regulatory approval, taking into consideration the likely patient	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			population covered and comparators used in most MS. Secondary PICOs may be incorporated based on HTD knowledge of likely but common requirements of MS and how new technology will be positioned within health systems. **Step 2**: Assessor/co-assessor, together with patients & HCPs representatives, review the HTD proposal and develop a draft PICO to be used as a basis for Member State survey. MS to respond to survey and suggest amendments to draft PICO with rationale. **Step 3**: Assessor/co-assessor consider survey responses and propose the final draft PICO, together with input from EU patients and HCPs. **Step 4**: Scoping Meeting between HTD meeting with Assessor/Co-Assessors (and representatives of the Coordinating Group sub-group JCAs) to finalise PICO, to allow the HTD to ask clarifying questions, to explain its position, discuss data availability and the range of appropriate methodological analyses. **Step 5**: Final assessment scope is communicated to the HTD and will form the basis for the submission dossier for the assessment. Any divergent recommendations and input gathered during the PICO survey with MS should be made visible to the HTD, to allow them to prepare for potential requests for local complementary submissions (thus providing predictability both for HTDs and MSs).	
Mihai Rotaru - EFPIA	General		We recognise one concern with starting the process early may be due to late EMA label changes. However, HTDs consider that the main process should not be designed to manage what we will know to be exceptions rather than the rule. The vast majority of EMA approved products do not require a late change to the label that is both material to JCA process *and was unanticipated* by the HTD. EFPIA is confident that its member HTDs can accommodate potential material changes to the EMA in a timely manner during the JCA process. As such further consideration should be given to developing a separate process for handling the small number of late label changes, as the benefits of starting earlier for the vast majority of products will outweigh the inconvenience of the exceptional cases.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Mihai Rotaru - EFPIA	General		Patients and Healthcare Professional organizations should be actively targeted and engaged at the EU level during the scoping and PICO development step of the process (see Step 3 above). Direct patient and HCP participation (e.g. scoping e-meetings) should be preferred over open and pro-forma calls for comment to encourage a more meaningful level of engagement and input. The current proposal limits their participation to the national level during the PICO survey. Whilst EFPIA is supportive of this, we are concerned that the compressed timeline may make meaningful engagement difficult in many MS, and that a structured engagement strategy at the EU level may be both more efficient and effective.	
Dr Daniel Widmer UEMO	General	-	Very good document. GPs applaud the idea of a non-data-driven scoping process, founded on national policy questions. GPs applaud the choice of non-drug interventions (for example psychotherapy, but also counselling and therapeutic education) as comparators (l. 209). With the example, the complex elaboration of PICO is enlightened. How GPs can integrate in the PICO process necessitate a more developed comment, actually in preparation.	
Dr. Thomas Ecker, Ecker + Ecker GmbH	general	-	Ecker + Ecker GmbH, a healthcare consultancy based in Germany with strong expertise in the early benefit assessment, welcomes the establishment of a European Health Technology Assessment (HTA) fostering closer cooperation between member states on health technology assessment by introducing a permanent framework for this joint work. The legal requirements for a European HTA have been determined as a legislative act by the end of 2021 with the EU regulation 2021/2282. From 2025, before placing innovative medicinal products on the market, oncology products and ATMP are subject to a European joint clinical assessment. In the next step, Orphan Medicinal Products (OMPs) will follow beginning in 2028 and from 2030, all medicinal products will have to go through the European assessment. While the regulation does not come into force until 2025, the process of implementation is already ongoing to ensure effective application from January 2025 onwards. At present, the development of a methodology for joint HTA work is facilitated by the European Network for Health Technology Assessment (EUnetHTA) 21 consortium.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			On May 2, the EUnetHTA 21 draft deliverable "D4.2 – Scoping Process – Practical Guideline" was published and is now available for public consultation. Within the European HTA, the scoping process determines a set of research questions that together define the overall assessment scope. Therefore, the draft deliverable "D4.2 – Scoping Process – Practical Guideline" (as of May 2022 in version 0.3), represents an essential guideline that provides a first concept for the development of a PICO framework reflecting the needs of all member states. While the guideline establishes an initial framework, we express our concerns regarding a number of aspects in this draft deliverable that should be specified in order to facilitate a structured and evidence-focused HTA process. These major aspects are summarized below: • **No concrete timelines specified for the scoping process:** – Start/initiation and completion of the scoping process – Timepoint of communication of consolidated PICO schemes to health technology developers (HTD) – Consequences of regulatory clock stops on European HTA timelines – Influence of labelling changes on European HTA timelines: A detailed concept for handling of labelling changes including corresponding timelines has to be developed. – Timelines for the scoping process in case of type-II variations • **No involvement of HTD in the scoping process is planned** – The current lack of exchange between HTD and European HTA bodies is a major point of concern. Exchange between HTD and European HTA bodies within the process of PICO definition (as already established as part of Joint Action 3) is crucial. – Therefore, HTD should be involved in the early stages of the scoping process to facilitate the identification of the assessment scope including the PICO elements that meet the needs of the involved HTA agencies with respect to the available evidence. Thus, scoping meetings with HTD should be incorporated to discuss the PICO	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			scheme(s) and related open issues. Overall, the procedure must ensure the broad involvement of HTD. • **No clear rules defined for development of PICO schemes** – A detailed methodology for defining and streamlining the assessment scope is needed including principles for choosing a core set of comparators based on a medical rationale, as well as for dealing with multiple PICO requests by the member states. In the current draft guideline, PICOs requested by member states are mainly driven by national policies and the determination of final PICOs seems to be purely based on majority vote. – So far, no clear rules have been defined for determining PICOs: o Off-label products are currently not excluded as comparators. o Multiple population & comparator requests are possible, with no limit on the number of requested PICOs. Here, a defined process for streamlining of multiple requests is required. – Identical PICOs should be applied for medicinal products in the same indication in order to ensure a uniform assessment of medicinal products within an active substance class. – Validity of PICOs not only for the European HTA but also for national assessments: A PICO scheme requested by a member state for the European HTA should also be applied on a mandatory basis at the national level later on. Consequently, the validity period of the PICO schemes should be addressed in the guideline. • **Lack of transparency in the scoping process** – Currently, the guideline indicates that only consolidated final PICOs are communicated to HTD. Knowledge of requested PICO schemes of member states is crucial for HTA, pricing & reimbursement on national level.	
Prof. Matthias	general		Comment:	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)			The current draft does not contain any information about the consequences of a MS not submitting its PICO requirements in time. In case this happens, it is imperative to avoid negative consequences (e.g., shorter timeline, additional national HTA) for the HTD. We recommend to set the deadline periods precisely (cf. comment to page 9, line 156) and to specify the consequences of a MS not submitting its PICO requirements in time.	
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)	general		Comment: Although not included in the EU-HTA regulation, orphan drugs are granted important privileges in some national assessment policies (e.g., Germany). On the one hand, the well-founded justification for the special position of orphan drugs rests in the setting of an economic incentive for pharmaceutical companies to pursue the development of drugs for rare diseases despite the economic risks, as often only insufficient therapy options are available in these indications. On the other hand and in addition to a guaranteed additional benefit, the obligation to submit certain data, such as large-scale subgroup analyses, may be eliminated, as the limited patient populations are generally insufficient to conduct large-scale RCTs and enable reliable analyses with the necessary power. In turn this could reduce the scope of the submission dossier and its assessment effort. We recommend to point out to the MS in the present sub-deliverable that they should adapt the scope of the requested evidence (PICO and additional information) to any orphan privileges existing in their country.	
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)	general		Comment: Will it be possible for HTD to provide the information needed for the scoping process earlier and thus start the process earlier and be informed about the consolidated PICO(s) earlier?	
Sebastian Werner vfa	general		The guideline does not include a **meaningful involvement of HTD** in the scoping process or in the validation of the PICO. A F2F or online scoping meeting with the HTD should be included to allow clarifying questions, to explain its position and data availability and discuss the range of appropriate methodological analyses to assess the parameters included in the assessment scope. The implementation of a scoping meeting with the HTD would be consistent with the past practice in EUnetHTA assessments and current practice in Germany as part of the dossier consultations. In both instances the scoping meeting revealed large benefits for the HTD, the assessors and the process in general. Hence, the **scoping meeting with the HTD has**	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			proven very useful in the past and must not be abolished. The implementation of a scoping meeting is also consistent with the regulatory framework of the HTAR, that establishes a similar involvement of HTD, patients and clinical experts in the scoping process [Article 8(6)]. Hence, the JCA CSCQ Meeting that involves patients and clinical experts for PICO validation could similarly involve the HTD. However, a separate HTD scoping meeting ahead or after that step is likewise possible.	
Sebastian Werner vfa	general		The guideline proposes an algorithm for the **definition of the assessment scope** based on a PICO survey of the MS and a subsequent consolidation process, which aims at minimizing PICO. Although the concept comprises a consolidation step, the algorithm will produce a **multitude of PICO questions**. This is because the concept does not assign an important role to the hypothesized (evidence driven) PICO of the HTD and does not aim at harmonizing the PICO across MS. Instead, it aims at a simple collection of MS PICOs, which are subsequently minimized towards the lowest number needed to satisfy the requirements for all MS. The proposed consolidation process is per se problematic, as it **potentially excludes relevant comparators** leading to exclusion of high-quality evidence (RCTs) from the European assessment. Further, the concept will not produce a manageable set of PICO. Given the very compressed timelines for evidence submission, Dossier preparation will **not** be **feasible** with a large number of PICO, with different populations and subpopulations and multiple comparators that needs to be addressed with indirect comparisons. Therefore, the concept for the scoping process and the consolidation process must be fundamentally revised. The concept should assign a greater importance to the evidence generated by the HTD for the definition of the PICO and include principles that can drive harmonization. The scoping process must streamline the MS questions and **aim for a harmonized European PICO** that is guided by the generated evidence of the HTD. The starting point for the scoping process should be the **research question of the HTD** using the approval studies. In the letter of intent, the hypothesized PICO for the assessment	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			should be provided by the HTD and should be used as a basis for MS PICO survey. Assessor/co-assessor should then streamline the survey responses and propose the draft PICO that should be finalized in a scoping meeting with the HTD. The PICO survey of the MS and the process of streamlining of the survey responses should apply **principles of harmonization** for the definition of PICO: 1. The definition of the PICO, especially of the relevant population and comparator should be based on the clinical evidence and **European** evidence-based guidelines 2. A possible clinical exchangeability of comparators should be consistent across **European** MS. 3. Overlapping research questions across **European** MS in terms of population/subpopulation should be conjointly evaluated as part of the same PICO Changing the scoping concept to assign a greater importance to the evidence generated by the HTD for the definition of the PICO in combination with the inclusion of principles of harmonization, the number of PICO can drastically be reduced, without potentially excluding relevant comparators (with high-quality evidence) and ensuring a feasible process for dossier submission.	
Sebastian Werner vfa	general		The guideline should provide clarity and transparency around the scoping process, including timing. **Clear definitions of binding timelines** for the scoping process should be made, especially about the time point when the final PICO is provided to the HTD. For HTD it is essential that the scoping takes place at an as early as possible timepoint, which ensures enough time for preparation of the dossier. The scoping process should begin at the start of the regulatory process (with the letter of notification of the HTD to the Coordination Group) and end 30 days later with the provisioning of the final scope to the HTD. This would ensure a period of **4.5 months for dossier preparation** for the HTD to submit a complete dossier in the standard approval procedure. This is a challenging short period, given the experience from Germany where dossier preparation of the HTD usually takes 9 to 12 months. Dossier preparations within such short time frame are only manageable through prescient scenario planning based on joint scientific consultations that are reliably used for the scoping process and JCA. Thus, the access of HTD for joint scientific consultations must not be limited. The availability of joint	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			scientific consultations must be sufficient to meet demand and be equipped with adequate capacities. A 4.5-month period for dossier preparation must be ensured for the HTD to submit a complete dossier.	
Sebastian Werner vfa	general		The guideline describes the PICO survey as crucial element for the final assessment scope. It is important to ensure **transparency** about the **PICO survey**, incl. the input gathered during the PICO survey by the MS, how the PICO was agreed by the HTA bodies, or about possible divergent recommendations. The information of the PICO survey should be provided to the HTD at time of scoping, to be able to prepare for potential complimentary requests and submissions at the national level. For more transparency, the information about the PICO survey should additionally be published in the JCA report as to give other HTD the opportunity to understand the individual MS needs.	
Sebastian Werner vfa	general		The authors point out the limitations of the usefulness of JSC recommendations for the scoping. The guideline lacks a description of the importance of the JSC for European HTA. The guideline should highlight the importance of a **reliable use of the JSC for scoping**. Changes of the JSC recommendations should be carefully considered and well justified. The availability of joint scientific consultations must be sufficient to meet demand and be equipped with adequate capacities.	
Sebastian Werner vfa	general		**Changes in label** can have a strong impact on the clinical assessment in Germany as data requirements can substantially change. According to a vfa survey, in approx. 8%-12% of the procedures in Germany a relevant change in the label occurs that lead to a substantial change in data requirments. A separate procedure must be put in place to deal with cases of labelling changes. The detailed timelines and changes to the standard procedure needs to be clarified. It should be also clarified how the cooperation between assessor/co-assessor and regulatory team can mitigate the risk of labelling change.	
Sebastian Werner	general		Article 8, sentence 6 of the HTAR states that the assessment scope shall be inclusive and shall reflect member states needs in terms of parameters and of the information, data,	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
vfa			analysis and other evidence to be submitted by the HTD. The guidance document does not refer to **"other evidence"** needed by the member states. For clarification a description and a process for handling of these "other evidence" should be given in the guidance document.	
Sebastian Werner vfa	general		Scoping may be new for some european HTA bodies. The HTAR does not provide a **definition for scoping**. To have a common understanding of scoping and the individual steps seen as integral parts of the scoping process, definitions for scoping and the scoping process should be provided.	
Sebastian Werner vfa	general		The preparation of dossiers is not feasible with a large number of PICO questions in the very limited time available. Even in the case that a European PICO or a manageable set of PICO can be agreed upon, the timely **preparation of a complete dossier** by the HTDs will be extremely challenging. According to a vfa survey, dossier preparation by the HTDs for the German HTA procedure takes 9-12 months. The currently discussed timeframe for dossier preparation by EUnetHTA21 is approx. 2 months. To ensure that the HTD can provide complete and high-quality data submissions for JCA, HTD must prepare far ahead of scoping. New instruments are needed to give the HTD the opportunity for consultations on the scope of the JCA even before the time of EMA submission. Hence, **Joint Dossier Consultations (JDC)** should be established, to ensure advice on the scope of JCA and the appropriate methodological approaches at the request of the HTD **before the time of EMA submission**. In that way the HTD could prepare the dossier based on a dossier consultation anticipating the final scope of the JCA that is determined later as part of the scoping process for JCA. In Germany, such consultations on data requests are usual practice and show large benefits for the HTD, the assessors and the process in general. Joint Dossier Consultations would strengthen the quality of HTA and would lower the risk of incomplete dossiers that potentially delay patient access.	
Matias Olsen, EUCOPE	General		It is important for the transparency and reproducibility of the process that the practical guideline defines clear rules and timelines for determining the final PICO(s) for the	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			assessment. The project plan for this deliverable states that the first objective is to provide a practical guideline on how to develop the PICO question(s). It further states that "…European PICO questions have to be formulated in a way that meets the needs of most countries. As a consequence, a European assessment might contain information that is relevant for some, but not necessarily other countries. We understand from this that the European PICO might not in practice reflect the need of every MS. Despite this, the practical guideline almost exclusively covers steps of the proposed MS PICO survey and does not provide sufficient detail on the methodology for consolidating the requested PICO schemes by MS, despite relevant existing EUnetHTA guidance being identified in the project plan. It is of crucial importance that the guidance document establishes a clear timeline and that the methodology and process for consolidating the PICO(s) is transparent. Recital 12 of the Regulation on health technology assessment (EU) 2021/2282 specifies that "Joint work should be produced following the principles of good administrative practice, and it should aim to achieve the highest level of quality, transparency and independence.". We have provided individual comments to address this aspect throughout the document.	
Matias Olsen, EUCOPE	General		The role of the HTD in the scoping phase needs to be clarified and addressed in the guidance document. Article 4 (4) of the Regulation on health technology assessment (EU) 2021/2282, specifies that the specific methodological and procedural guidance that shall be developed for medicinal products, medical devices and in vitro diagnostic medical devices shall take into account, where appropriate, the methodology developed by EUnetHTA Joint Actions. In EUnetHTA JA3 the PICO was developed with input from the HTD, in the form of a letter of intent, as well as an in-person scoping meeting with the assessor, before final PICO(s) for the assessment was defined. In general, existing EUnetHTA guidance documents reflect the involvement of the HTD in the definition of the PICO. For example:	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			The guidance document "Comparators & Comparisons: criteria for the choice of most appropriate comparator(s)" is identified in the project plan as the guidelines that describe scenarios that often occur when choosing comparators and states that those can be used as a starting point for the current project. This guideline states that "…in the majority of countries the product sponsor, clinical and patient experts, clinical guidelines and (international) methodological guidelines have an input on the choice of comparator. This needs to be reflected in this guidance document, and the role of the HTD in the scoping phase and identification of comparators needs to be specified. Additionally, the project plan states that the process steps to derive the European PICO questions were as an objective addressed in the "PICO concept paper, 2020". This guidance which was only recently made public (as of 4 April 2022 it was not made available to us when we contacted the EUnetHTA 21 secretariat), describes the role of the HTD in the scoping process, consisting of the HTD proposing a PICO with a letter of intent, the HTD being provided the option to comment on the preliminary PICO question(s) and of a scoping F2F meeting with the HTD to discuss the proposed consolidated PICO(s) and potential label changes. We have provided individual comments to address the role of the HTD at various points of the scoping process in the document.	
Matias Olsen, EUCOPE	General		In particular, the following should be specified in the guidance document: Population: •The patient population should be defined in accordance with the (draft) SmPC. Intervention: •The intervention should be defined in accordance with the (draft) SmPC. Comparator: •When the comparator is a medicinal product, it must have a marketing authorisation for that indication and line of treatment. •Pharmaceutical compounds that are used off-label should not be included as comparators	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			when an authorised alternative exists for that indication or line of treatment. •The procedures for resolving the issue of multiple comparator requests from MS must be transparent and communicated to the HTD (especially in cases, where all listed comparators are required, so called "AND" situation). •A maximum choice of comparators should be defined in the guidance document, in order to not overburden the procedure. The comparator should represent the current state of medical knowledge, and should be determined based on international standards of evidence-based medicine and preferably European treatment guidelines and in exceptional circumstances, international or national guidelines.	
GSK	General	General	HTDs have no role or ability to provide any input into the scoping process.	
GSK	General	General	Given the specificities of vaccines and national immunisation programmes (NIPs) with regards to the PICO scoping process (see comments below), we suggest to specify in the PICO scoping process guideline that it will account for vaccines specificities, i.e. a similar statement such as done for medical devices for the PICO scoping process (see doc Scoping Process project plan D4.2 v1.0)	
Roche	General		Article 8, clause 6 of the HTAR states that the assessment scope shall be inclusive and shall reflect member states needs in terms of parameters and of the information, data, analysis and other evidence to be submitted by the HTD. The guidance document does not say anything about the **other evidence** needed by the member states. For clarification, the handling of this "other evidence" should be described in the guidance document.	
Roche	General		Article 8, clause 6 states that the scoping process shall take into account information provided by the health technology developer and input received from patients, clinical experts and **other relevant experts**. The guidance document does not say anything about the involvement of "other relevant experts" nor is a definition of these other relevant experts for the scoping provided.	
Roche	General		Scoping may be new for some european HTA bodies. The HTAR does not provide a definition for scoping/scoping process. To have a common understanding of	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			scoping and the individual steps seen as integral parts of the scoping process, definitions for scoping and the scoping process should be provided.	
Advanced Medical Services GmbH	general		Provide the different process steps with clear timelines / time points applicable for EUnetHTA 21 and HTAR, respectively.	
James Ryan, AZ	General		The proposed scoping process assumes that all needs from all Member States are required at a European level. However, the Regulation also provides additional context, which suggest that whilst Member States need to be considered, not all need to be included. "Member States should be able to perform **complementary clinical analyses**, which are necessary for their overall national HTA process, on the health technologies for which a joint clinical assessment report is available. In particular, Member States should be able to perform **complementary clinical analyses relating, inter alia, to patient groups, comparators or health outcomes other than those included in the joint clinical assessment report**" The proposed scope recommends an additive approach, removing duplication, rather than a consolidated approach focussing on those areas that are common across several or all Member States. An additive approach, as described, for an overall European assessment risks disproportionate time spent on analyses that may have limited impact on the majority of Member States or the majority of EU patients. Furthermore, it risks having many redundant analyses that are requested through the additive approach but not actually requested by any Member State. For example, there may be just one Member State that requires an analysis in a single sub-population and for three outcomes. However, another country may ask for analyses in 20 different outcomes for the overall population only. In this case, these 20 additional outcomes have to be provided in the single sub-population even though they have not been requested. To deliver a high quality, timely and meaningful report, ensuring a proportionate amount of resource is allocated relative to the EU patient population treated, a clinically, evidence-	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			based scoping methodology should be applied, supplemented by complementary analyses at a Member State level. This will ensure that a consistent PICO framework will be applied across assessments, as well as focus the European PICOs on those key common areas that impact the majority of EU patients, whilst maintaining Member States' right for additional PICOs and associated complementary analyses addressing their own individual needs.	
EFSPI	General		We are generally concerned with the limited involvement of the HTD in the scoping process. This pertains both to the limited options for consultation and the to limited options of provision of information by HTDs to support the selection of PICOs. We see no issue with increased involvement of the HTD, as long as this is done a transparent manner. Indeed, the HTD will be in a unique position to provide information relevant to effectively and efficiently bridge available studies conducted by the HTD with the potential scope. Failure to integrate the expertise of the HTD regarding the Benefit/Risk of their own product will conflict with the aims of the HTA regulation, to ensure high-quality assessments and timely availability of innovative medicines and health technologies for patients. We encourage that the scoping process is modified to include interactions (scoping meeting) between assessors and co-assessors, member states and HTD representatives to review the scientific aspects of the scoping and PICOs, including review steps in the PICOs development and consolidation process to obtain input from HTD and member states.	
EFSPI	General		The draft guideline suggests that scope of the assessment of an intervention should not be data driven and that research questions should not be deduced from the available studies. While it is important that the scope is not ***defined*** by data availability, it should be acknowledged that available cumulative studies are key to ***informing*** the full scope. Insisting otherwise would ignore the comprehensive/cumulative evidence-based approach reflected in the development program for the health technology under assessment. In turn, this would adversely impact the aim of the HTA regulation to ensure timely availability of innovative medicines and health technologies for patients. For example, a member state may request a specific comparator within a class that was not included in the pivotal trials. However, if the pivotal trials instead included an exchangeable comparator from the same class, that might be an acceptable alternative for the member	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			state. It is critical that the scoping process directly facilitates this kind of alignment to ensure an effective and efficient development program and assessment. Accordingly, we encourage that the following modifications are considered for the scoping process: 1. That it it is acknowledged that data availability/feasibility must be as part of the scoping discussions to facilitate effective and efficient joint clinical asessments 2. A template for a 'Letter of Intent' is developed incorporating a minimal set of requirements alongside optional components providing the HTD with the option to provide information that can help member state to complete PICO surveys. A template framework could be developed based on the learnings during EUnetHTA21, with input from all stakeholders (including HTDs) That data availability/feasibility is carefully considered at key steps during the scoping, including during PICO validation, and HTD input should be elicited as part of the scoping process.	
EFSPI	General		The draft guidance indicates that member state needs should be translated to the lowest number of PICOs possible. At the same time, no preliminary PICOs will be provided prior to member states to the PICO survey, and there are very limited options for HTD to provide information to support member state selection of PICOs. We are concerned that this open-ended format can lead to a very large number of PICOs in practice. This in turn raises concerns about overinterrogation of data and statistical multiplicity issues. With the large number of post-hoc statistical analyses needed to address many different PICOs, there is a real risk of generating confusion among HTA bodies, prescribers, and patients. The issue is compounded by the fact that the assessment of each PICO will be visible to all member states. For example, if two different member states request two different but related PICOs (for example, they might select slightly different subpopulations from within a pivotal trial), conclusions across such two related PICOs may appear conflicting due to random chance. To reduce the multiplicity issue, scoping should not be detached from the clinical trials reflected in the regulatory submission to EMA. For example, if a proposed PICO is only a slight variation of a subpopulation pre-specified in a clinical trial, it may be an acceptable trade-off for the member state to use that pre-specified subpopulation instead. Member	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			states should be encouraged to evaluate feasibility of aligning to a priori definitions in the clinical trials of (sub)populations, subgroups, background therapy. Importantly, they should be provided with input from the HTD to be able to evaluate this feasibility during scoping. It is also recommended that as part of the validation step for the PICOs, due consideration is given to issues around multiplicity.	
EFSPI	General		The draft guidance does not provide any considerations in relation to the concept of estimands. Estimands are increasingly important in clinical trials that are used for regulatory purposes, as described in detail in ICH E9 (R1). They provide a framework to be precise about the scope of the clinical question of interest that extends the PICO framework, incorporating also the summary measure used to compare interventions, as well as intercurrent events that may affect the interpretation of outcome of interest. Intercurrent events are also highly relevant for HTA, not least to address specificities that may arise when translating national policy questions into research questions. For example, an estimand addressing the treatment effect if patients do not initiate a certain rescue medication may be of interest in a member state where that particular rescue medication is not part of usual care. We acknowledge that estimands are not yet widespread in HTA. However, regulatory focus on estimands will only increase in the years to come, and estimands will be a key part of both the protocol and statistical analysis plans of future trials. Thus, it is critical to acknowledge the notion of estimands to appropriately guide assessors. We recommend that, as a minimum, a subsection is added to section 8, clarifying that available studies may describe the clinical question(s) of interest in terms of estimands, and that it needs to be carefully considered how the scope implied by such estimands relates to the scope of interest for the JCA.	
EFSPI	General		Currently, many member states have HTA processes that occur later in time and rely on information provided from the HTA processes of members states that begin the process early, and from HTA processes that are outside the EU (e.g. UK-NICE, CAN-CADTH/INESS, and AUS-PBAC). With the EU HTA regulation, these member states will now be undertaking PICOs scoping in	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			parallel with these other earlier HTA processes. What support will be given to member states in the early years of implementing the new EU HTA regulation to help them with the scoping process, and ensure that their assessment is focused on evidence-based evaluation of their country specific needs?	
EFSPI	General		Further guidance on the expectations for Systematic Literature Reviews (SLRs) use for HTA and PICOs (e.g. type of SLR [rapid, full], level of quality, scope, cut-off timeframes for different countries…) would be beneficial	
Vaccines Europe	general		Given the specificities of vaccines and national immunisation programmes (NIPs) with regards to the PICO scoping process (see comments below), we suggest to specify in the PICO scoping process guideline that it will account for vaccines specificities, i.e. a similar statement such as done for medical devices for the PICO scoping process (see doc Scoping Process project plan D4.2 v1.0)	
Alexandra Poulsson, Norwegian Institute of Public Health	Throughout the guidance 13-17 19 21	- Table 3-8 Figure 5.1 & e.g. line 391	Where for example "fully licensed indication" is used to describe medicinal products it should also state for example "fully approved intended use" in order to be relevant for medical devices.	
AIM – International Association of Mutual Benefit Societies	General		In general the document is balanced and can be conducive to better generation of data on added therapeutic value. The methodology, that starts with the research-relevant questions and not from the available data, is balanced and makes sense.	
AIM – International Association of Mutual Benefit Societies	General		It would be interesting/relevant to undertstand the timeframe when the PICO should be requested from the HTD	
AIM – International Association of Mutual Benefit Societies	General		In general, the question of the dosage of the medicine is not really mentioned or addressed in the document. This question should be mentioned in the intervention part, especially if different populations receive different dosage forms. Dosage should not be left to the "additional information" section.	
AIM – International	General		Stakeholder involvement is left unaddressed in the document. Stakeholders should receive at least the PICOs when they're validated and shared with the HTD.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Association of Mutual Benefit Societies				
Tanja Podkonjak - Takeda Pharmaceuticals International AG	General		We note that the current scoping guidance does not provide a proposed timeline. Scoping should be initiated at a time point that allows sufficient time for the consolidation of the European PICO, exchange with stakeholders, in particular the HTD and patient and clinical experts, and prepration of the JCA dossier in line with the EU PICO. From past industry experience with EUnetHTA Joint Action 3 (JA3) and the timeline to prepare current individual Member State (MS) HTA submissions, we recommend the scoping process be initated at the point of EMA acceptance of the regulatory dossier and the request the final scope be communicated to the HTD a **minimum of 5 months** prior to CHMP opinion. Given the JCA submission deadline of 45 days prior to CHMP opinion, this would leave the HTD approximaltey 3.5 months for dossier finalisation, which will be challenging particularly for complex disease areas (i.e. oncology and rare diseases). Any less time risks the HTD not being able to prepare the required analysis and data for a robust JCA. Given the complexity of HTA submissions and the geographic coverage of an EU JCA submission (with different treatment guidelines), it is vital that the HTD be given sufficient time from the communication of the final scope to the submission deadline. This will enable the HTD to properly conduct the requested analyses and submit a high quality JCA dossier which in return will reflect on the final JCA report. Takeda recommends the scoping process be started upon the acceptance of the EMA submission to allow sufficient time to gather input from Member States (MS), patient and clinical experts and the HTD. This will also allow for the assessors to have adequate time to consolidate the MS responses and develop a pan-EU PICO. We note the proposed 2-week turn around period for the PICO survey by MS. Given current national HTA scoping processes, we are concerned about the feasibility of this timeline for MS to complete the survey and include patient and clinical input. Takeda suggests the timeline for scoping be reconsidered to enable a thorough and representative process from all stakeholders.	
Tanja	General		A separate procedure should be put in place to deal with last-minute changes to the final	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Podkonjak – Takeda Pharmaceuticals International AG			EMA label. Last minute or unexpected label changes, many which occur near the end of the EMA review, remain the exception rather than the rule and a separate process to handle them is more appropriate than defining a less-than optimal 'standard' process to fit all assessments. We request a process be developed and clarified for these exceptional situations and suggest a similar process to the existing EMA 'clock-stop' be introduced to allow for sufficient time for revisions to the JCA dossier and supporting analyses.	
Tanja Podkonjak – Takeda Pharmaceuticals International AG	General		Patient and clinical experts, or their organisatoins, should be engaged early and proactively in the EU scoping phase. A structured process and methods of eliciting input from patient & clinical experts should be developed and standardised to ensure input into the scoping stage from these key stakeholder is meaningful and consistently sought as a permanent part of the future JCA process. We recommend developing a standard process (i.e. including a scoping meeting and input document or table similar to the MS PICO survey) be co-developed with patient and clinical organisation. A standardised process of eliciting input should be employed over an open call for feedback from patient and clinical experts as this will ensure a more meaningful contribution to the PICO development at EU level. Furthermore, Takeda is concerned that the suggested 2-week timeline for MS to complete the PICO survey, including gathering local patient and clinical feedback, may not be feasible. Such a short time frame risks no patient or clinical input being included and therefore a PICO survey response which is not informed by experts and potentially not representative of local clinical practice. We request the current timeline for MS and expert input into the scoping process be reconsidered as described in the timeline comment. Finally, Takeda requests consideration or a program be given into training patient and clinical experts on the new EU JCA process (including the scoping stage) and the principles of Health Technology Assessment (HTA). This will empower patient and clinical experts to be active participants in the JCA process and as a result yield a higher level of input into the JCA process.	
Tanja Podkonjak – Takeda	General		Following experience from EUnetHTA JA3 and practices from current national HTA scoping procedures (i.e., Ireland, Germany, Portugal to name a few), Takeda strongly recommends the scoping process be revisited to allow for meaningful involvement from all key	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Pharmaceuticals International AG			stakeholders, including the HTD. HTD involvement in the scoping process is standard procedure in most current EU national HTA processes, either was formal scoping meetings or informal advice, and is valuable in resolving queries on the intervention, data availability and the treatment landscape ultimately resulting in improved efficiency of the HTA process. An inclusive scoping process be developed which contains the following process steps: - The JCA process initiated with a 'letter of notification' submitted from the HTD to the Coordination Group upon acceptance of EMA submission. We propose the letter of notification outlines the characteristics of the technology as well as the intended PICO (hypothesis) for the assessment. - Following the MS PICO survey, a scoping consultation should take place either in person or online and should include patient and clinical experts as well as the HTD. This would enable the assessor and co-assessor to ask the HTD clarifying questions on the technology and proposed PICO, and the HTD would be able to explain the data availability for the research question. During this meeting the range of appropriate methodological analyses could be discussed to assess the parameters included in the assessment scope. This step would improve efficiency of the JCA process as the HTD would be informed of the expected analysis and the assessor/co-assessor would be aware of the existing data and be informed of the anticipated analyses which will be submitted in the JCA (and if needed secure resources from the Technical Experts Network). - Transparency and rationale about how the final EU PICO was agreed by the assessors should be shared with the HTD. Divergent requests input gathered during the PICO survey by MS and their rationale should be made visible to the HTD to allow to prepare for potential complimentary (unavoidable) request and submissions.	
Tanja Podkonjak – Takeda	General		Takeda raises concerns on the proposed process of establishing the EU JCA PICOs based on policy decisions at a MS level as this may lead to multiple PICOs. The potentially high number of PICOs will limit the feasibility of submitting a full dossier within the proposed timelines. Multiple PICO will require analysis informed with indirect treatment comparisons (ITC) within many subgroups which may have limited scientific validity and introduce uncertainty. The multiplicity of PICOs may require that many sections of the JCA dossier are informed by evidence with lower acceptability. There is a risk	

<table>
<tr><th>Comment from</th><th>Page</th><th>Line/ section number</th><th>Comment and suggestion for rewording</th><th>Editorial comment?</th></tr>
<tr><td></td><td></td><td></td><td>that it will not be possible for the HTD to address or submit data for some of the PICOs, leading to unclear implications on the continuation of the assessment and its usefulness by MS for decision making.

A potentially high number of PICOs will also exponentially increase the number of ITC required for the assessment, and EUnetHTA21 Methodological Guideline D4.3.2: Direct and Indirect Comparisons makes clear statements towards the less desirability of ITC methods.</td><td></td></tr>
<tr><td>Matias Olsen, EUCOPE</td><td>12-19</td><td>232-348</td><td>In the current consolidation process, the decision for the final PICO schemes is solely driven by majority: if the majority of countries requests a certain comparator, this comparator will be selected. However, this decision should be based on current medical knowledge.

Moreover, in the draft guideline, handling of the following scenario is not discussed:

Table 1: Exemplary list of submitted comparators
<table>
<tr><th>☑ Member State 1</th><th>☑ Member State 2</th><th>☑ Member State 3</th></tr>
<tr><td>☑ Comparator(s)
☑
☑ Could use any of /all required</td><td>☑ Comparator(s)
☑
☑ Could use any of /all required</td><td>☑ Comparator(s)
☑
☑ Could use any of /all required</td></tr>
<tr><td>☑ Comparator 1</td><td>☑ Comparator 1</td><td>☑ Comparator 1</td></tr>
<tr><td>☑ Comparator 2</td><td>☑ Comparator 2</td><td>☑ -</td></tr>
</table>
In the scenario depicted in Table 4 comparator 1 would be selected as comparator of the resulting PICO scheme.

However, first of all, this approach does not take into account whether comparator 2 might represent the more suitable treatment from a medical, evidence-based point of view (e. g. this treatment is recommended in recent clinical practice guidelines as new gold standard due to superiority, whereas comparator 1 might reflect a well-established treatment but is inferior to comparator 1). Therefore, this approach might result in favoring outdated treatment options. Secondly, in the current draft guideline, it is not specified, whether, in cases, where only evidence for comparator 2 is available, this evidence will still be considered for the assessment (in our example for the assessment of member state 1 and member state 2). For</td><td></td></tr>
</table>

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			this reason, the availability of evidence should be considered in the consolidation process. Otherwise, this approach would result in loss of information rather than providing the best available evidence. In conclusion, the consolidation of PICO schemes should be driven by current medical knowledge. In particular, the choice of comparator must be based on available clinical evidence.	
GSK	9-11	3.1 PICO survey	**Specific feedback on vaccines** The guideline proposal assumes that scoping processes to define PICOs are in place in each of the EU 27 countries and thus each country able to participate in the survey to define PICOs. For vaccines, National Immunisation Technical Advisory Groups (NITAGs) should input to this survey as NITAGs are in almost all European countries involved in the assessment and recommendation for inclusion of a vaccination programme into the national immunisation calendar. However, in a recent analysis, only NITAGs in 7 EU MS were found to have a decision-analytic framework suggesting that currently not all NITAGs in the countries may apply a scoping process before assessment and recommendation. Further, HTD can only themselves submit dossiers in 14 out of 27 EU countries. Thus, during the further development and finalisation of this guideline, in particular from a vaccines point of view, feasibility of such a proposed survey including input from NITAGs should be assessed across EU 27. Reference Laigle et al. 2021 Vaccine market access pathways in the EU27 and the United Kingdom – analysis and recommendations for improvements - ScienceDirect Population: The licensed population, which the HTD is expected to specify at the start of the scoping process, may vary from the recommended target population of an NIP (policy question) (NIP and corresponding vaccination schedule can be a subset of the licensed population). For vaccines targeted at new disease areas no recommendation may exist but vaccines may also target disease areas with existing NIPs, thus it should be clarified whether for vaccines the licensed population or the target population & proposed schedule for an NIP should be specified by the HTD. As vaccination (e.g., recommendation and reimbursement status), target populations (e.g., age-based vs risk-based), vaccines (e.g., antigen composition; technology – e.g. conjugated vaccines vs polysaccharide vaccine), vaccination schedules (i.e., age-related timing and	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			number of doses administered) for NIPs targeting the same target population (e.g., infants/young children) vary across EU27, populations and comparators suggested for the national immunisation programme by the MS may considerably vary. Thus, the proposed consolidation approach to determine the PICO and sub PICOs is likely to result in a substantial number of PICOS creating a highly complex setting and thus likely limit feasibility of the dossier and assessment procedure.	
Matias Olsen, EUCOPE	9-10	160-172	In the current draft, no timelines are specified except for submission of the dossier. Specific timelines for all steps depicted in figure 3-1 should be determined. Add: **"The timeframe from receiving the letter of intent until final validation of PICO schemes must not exceed x weeks"**	
GSK	15-16	289-301	Should one apply a, b and c in order? For example, firstly check one comparator, then 'AND scenario, lastly 'OR' scenario.	
Matias Olsen, EUCOPE	11-12	203-214	By predetermining the use of PICO the HTD is limited to always provide comparative evidence even though there might be situations where it is not feasible or ethical to conduct comparative trials, e.g. rare diseases. Add: "**The PICO framework should consider the possibility where there is no pharmaceutical comparator at all, i.e. single-arm trials, and these situations will need to be considered in the JCA.**".	
Matias Olsen, EUCOPE	9-10	167-168	Figure 3-1 only refers to medicinal products, at present, no timelines for medical devices are specified.	
Edwards Lifesciences	6	93/ Section 1.2 Role of the PICO in the assessment	We believe that research questions could be general, but they should be linked to identifying and addressing the unmet need. Hence the application of PICO needs to be based on guidelines and expert opinions to address that unmet need.	
Paolo Morgese – ARM	6	93-99	ARM is concerned about the proposed approach and the impact on operational feasibility. A fair and viable scoping process should not be unidirectional (i.e. not based only on input from MS or HTAD) but the result of an inclusive process and taking input from all relevant stakeholders, including patient representatives and clinical experts.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
James Ryan, AZ	6	91-95	We agree that an appropriate translation of the national policy questions into research questions should be performed. However, it is important in formulating national policy questions to inform the MS PICO that these take account of the scope of the Regulation, specifically clinical assessment should be compared to the "best available alternative" in the Member State. Economic and certain other local P&R considerations are out of scope for the Joint Clinical Assessment. To enable this, and ensure the most appropriate response to the survey, the scope process needs to provide guidance to Member States in completing the proposed survey, as well as apply that guidance at a European level by the assessors.	
Matias Olsen, EUCOPE	6	92-95	Rather than focusing on national policy questions, the development of research questions should be driven by current outstanding medical issues. In particular, the choice of comparator should be based on the generally recognised state of medical knowledge. Moreover, the comparator used in the investigative study should be included in the list of comparators defined in the scoping process. Add: "Rather, an appropriate translation of national policy questions into research questions is performed during the planning stage of the assessment**, bearing in mind that the PICOs should be developed based on the available evidence and preferably European treatment guidelines, or national guidelines in exceptional circumstances."**.	
Mihai Rotaru - EFPIA	6	88-90	As per our introductory comment above, EFPIA recommends that the JCA adopt a European perspective with a focus on what is common to the MS health systems. The HTAR allows for what material differences that do exist between MS to be accommodated in subsequent local, complementary clinical analyses.	
Advanced Medical Services GmbH	6	88-90	HTAR, Article 8(6), last sentence: "The scoping process shall also take into account information provided by the health technology developer and input received from patients, clinical experts and other relevant experts." The "overall assessment scope" (consolidated and validated PICO) appears to be a black box	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			for outside parties (conflicts with the principle of transparency). We understand this as an internal process exclusively within EUnetHTA 21. Providing all information/tables of the national PICO surveys is desirable. A consolidated table should be complemented by rationales and details on the derivation of the final PICOs according to the Member States' requests and needs including input of patients, clinical/relevant experts at national level and its consideration; in this context references made to treatment guidelines are rather important.	
Silke Walleser Autiero Medtronic	6	78-80	It is noted in the draft guidance that 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 purpose of any HTA should indeed be to inform decisions concerning the allocation of budgetary resources in the field of health, for example in relation to establishing the pricing or reimbursement levels of health technologies and this is rightly noted in the Regulation. This principle for European HTA should be reflected in the scoping process, ie member states should be asked for the relevant policy question(s) they need to answer (and not just the PICO).	
James Ryan, AZ	6	88-90	We have a different interpretation on the Regulation related to the comment "that the assessment should cover the PICO(s) requested by the MS." One of the principles of the Regulation was to undertake joint work on common scientific, clinical aspects of HTA, suggesting that common elements of a PICO should be included, but not necessarily those where aspects may only be required by a few or even a single Member State. The Regulation also allows for the following "Member States should be able to perform **complementary clinical analyses**, which are necessary for their overall national HTA process, on the health technologies for which a joint clinical assessment report is available. In particular, Member States should be able to perform **complementary clinical analyses relating, inter alia, to patient groups, comparators or health outcomes other than those included in the joint clinical assessment report**"	
Paolo Morgese - ARM	6	88-90	ARM wishes to underline that while HTAR article 8(6) indicates that the assessment scope "shall be inclusive and reflect the Member States' needs in terms of parameters and of the information, data, analysis and other evidence…", it also states that "the scoping process shall also take into account information provided by the health technology developer". In	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			ARM view, setting up a process mandating selection of all requested PICOs is at risk of making the JCA inefficient and in some cases not manageable. ARM would like EUnetHTA 21 to take a pragmatic approach in PICOs' selection, taking case-by-case decisions based on science and input from MS, HTAD and also by patient representatives and clinical experts.	
Tanja Podkonjak – Takeda Pharmaceuticals International AG	6	88-90	Takeda understands that the compromise leading to the HTA Regulation (HTAR) has foreseen that the scope needs to be inclusive and reflect MS' needs. However, Takeda recommends that this paragraph be modified to qualify that the assessment scope should be sufficiently streamlined to represent a pan-European perspective but also enable the assessor/co-assessor to finalize the assessment within the deadlines inscribed in the Regulation as well as to enable the HTD to submit the full dossier with the highest level of evidence. The multiplicity approach in the current proposal whereby the EU PICOs is based on policy decision at a MS level, could lead to multiple PICOs requested in the EU JCA dossier. Takeda is concerned that a scoping process which results in a consolidated EU scope of multiple PICOs (i.e., as shown in Table 3-8 on page 19) would not be manageable to address by the HTD. Furthermore, this approach may request analyses which would focus on evidence with limited acceptability that do not reflect the value of innovation. The multiplicity of PICOs may end up with the JCA having many requested analyses and sections informed by lower level or in some instances no evidence.	
M. Ermisch – GKV-Spitzenverband	6	92 -93	The primary research question to be answered by HTA is the added value of a health technology in comparison with other new or existing health technologies (see recital 2 of the HTA regulation). With regards to the PICO, this means that the population needs to represent all of the patients that can be treated with the new technology on label, the intervention is the new technology, the comparator(s) are existing technologies that represent the MS standard of care and the outcomes are patient relevant health outcomes. Thus, the statement in lines 92-93 is of high relevance to both the assessment of medicinal products and the assessment of medical devices and must not be changed. In the past, the intended purpose of medical devices often exceeded the indications of the clinical trial results used for the conformity assessments, and it remains to be seen whether the setting of an intended purpose under the MDR will really follow stricter rules. It must be ruled out that the scope of the HTA would have to include research questions derived from any feasibility case series conducted with the medical device in question.	
Anna Lien	6	81	Unsure if PICO "parameters" is the most suitable term. Please consider to replace	x

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Espeland, Norwegian Institute of Public Health			"parameter" with "element". (applies to all mentions of PICO parameter in the document)	
Anna Lien Espeland, Norwegian Institute of Public Health	6	90	I suggest to clarify if the s in PICOs/PICO(s) is not for "study" or "study type" in this document, but is plural.	x
Tuomas Oravilahti, FIMEA	6	92	Agreed, in principle. However, the HTAR system focuses on new treatments and the outcomes for certain ATMPs for example can be quite exotic. Some parts of the very scarce data can be left out if PICO is formed blindly, rendering the assessment useless exactly when it is most needed. It should be understood that the company will present the results from the trials to the national systems, which must take a position on those results. In addition, it is likely that that the economic models will be based on the clinical trial outcomes, so they must be included in the clinical assessment. MS do not have the economic models available at the time of the PICO survey. Article 8(6): "-- -- -- The scoping process shall also take into account information provided by **the health technology developer** and input received from patients, clinical experts and other relevant experts."	
Dr Martin Danner BAG SELBSTHILFE	6	111	After "(Section 3.1)" should be added: "The patient organizations of the MS have to be involved in this process" The national perspective of the patients of the different MS on relevant subpopulations, the specific circumstances of the intervention, the choice of the relevant comparator an the definition of relevant outcomes (patient relevant or not) is very important to specify the data requirements for the assessments.	
Dr. Thomas Ecker,	6	92–95	**Statement in guideline:** *„By principle, the scope of the assessment of an intervention should not be data driven, that*	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Ecker + Ecker GmbH			*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*." **Comment:** Rather than focusing on national policy questions, the development of research questions should be driven by current outstanding medical issues. In particular, the choice of comparator should be based on the generally recognized state of medical knowledge and deviations from this procedure require justification. Moreover, assessments should consider the best available evidence to address the defined research questions. Therefore, the comparator used in the investigative study should be included in the list of comparators defined within the scoping process. In this way, the production of assessments, where there are no studies eligible for inclusion due to strict inclusion criteria, is avoided.	
Sebastian Werner vfa	7	104 / 1.3	The guideline states that the scoping process is initiated by JCA secretariat according to the timeframe for, and well in advance of, the JCA. **Clear definitions of binding timelines** for the scoping process should be made, and "well in advance" should be further specified. Clear definitions are necessary, especially about the time point when the final PICO is submitted to the HTD. For HTD, it is essential that the scoping takes place at an as early as possible timepoint, which ensures enough time for preparation of the dossier but also provides enough certainty about authorisation and indication wording. The scoping process should begin at the start of the regulatory process (with the letter of notification of the HTD to the Coordination Group) and end 30 days later with the provisioning of the final scope to the HTD. This would ensure a period of **4.5 months for dossier preparation** for the HTD to submit a complete dossier in the standard approval procedure. This is a challenging short period, given the experience from Germany where dossier preparation of the HTD usually takes 9 to 12 months. Dossier preparations within such short time frame are only manageable through prescient scenario planning based on joint scientific consultations that are reliably used for the scoping process and JCA. Thus, the	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			access of HTD for joint scientific consultations must not be limited. The availability of joint scientific consultations must be sufficient to meet demand and be equipped with adequate capacities. A 4.5-month period for dossier preparation must be ensured for the HTD to submit a complete dossier.	
Sebastian Werner vfa	7	114 / 1.3	The guideline states that 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 every MS. The scope is critical for HTD. However, the **results of the PICO survey** are also **essential for the HTD** to become aware of all the individual MS needs, incl. about the input gathered during the PICO survey by the MS, how the PICO was agreed by the HTA bodies, or about possible divergent recommendations. Hence this information of the PICO survey should be provided to the HTD at the time of provision of the final scope. Suggestion for rewording: *The final assessment scope is provided to the HTD, incl. the information gathered by the PICO survey in MS.*	
Edwards Lifesciences	7	104 / Section 1.3 Definition of the PICO(s) for an assessment	It is unclear whether the process is initiated by the HTD or by the EUnetHTA21 JCA secretariat? Or by the HTA coordination group? More visibility is required on who initiates the scoping process. According to the HTAR, the European Commission informs the HTD when their MD has been selected for assessment. The HTD shall then send a letter of information specifying the intended indication of the MD. Separately, there is a contradiction between the information on line 104 (”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.”) and the text in line 130 (page 9: “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.”)	
Edwards Lifesciences	7	109/ Section 1.3 Definition of the PICO(s) for an	Who will be responsible for receiving and responding to the PICO Survey at the MS level? For the sake of transparency this should be clearly defined, and we believe the names of the individuals and that of the organizations they represent should be publicly available.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
		assessment		
Norbert Gerbsch for IGES Institut GmbH and HealthEcon AG	7	105 / 1.3	**Comment:** According to section 3 "In EUnetHTA21 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". The fact, that starting the process is attributed to the HTD by initiating the scoping process is welcomed. The assessments according to REGULATION (EU) 2021/2282 will not be started by the HTD but „by the Joint Clinical Assessment (JCA) secretariat according to the timeframe for, and well in advance of, the JCA." It is however unclear at which point in time the process will start and what "well in advance" means. This is of extreme importance: The decisive step after PICO consolidation is the preparation of the dossier. The time between the communication of the final PICOs to the HTD and the deadline of the submission of the dossier (D-45, see Figure 3-1) might be short or even too short to meet all requirements. If the process is initiated by the JCA secretariat, there is no way for the HTD to ensure that enough time for preparing the dossier is provided by starting the scoping process early in time. Therefore a clear timeline should be attached to the scoping process in EUnetHTA21 to facilitate planning for all parties involved and it should be assured, that the secretariat starts the scoping process at the earliest possible point in time to ensure that enough time is left for preparing the dossier according to the PICO requirements. **Suggestion**: It is therefore suggested to add a mandatory duration and timeframe for the consolidation of the PICO scheme i.e. for example like "The consolidated PICO scheme must be communicated to the HTD X weeks [insert number of weeks] after the submission of a request for assessment".	
Roche	7	104-106/ 1.3	*"The scoping process is initiated by the JCA according to the timeframe for, and well in advance, of the JCA"* - this seems a bit vague. A clear timeline for this step in relation to other key JCA and/or regulatory milestones as well as its reflection in figure 3-1 would be welcomed. The HTD should have the opportunity to start the scoping process by himself with the submission of the letter of intent. This should include the possibility	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			for the HTD to submit the letter of intent as early as possible, e.g. with submission of the letter of intent to EMA.	
Roche	7	114/1.3	In addition to the final assessment scope, the individual PICO survey responses from all parties (e.g. HTA bodies, patients, clinical experts, etc.), including any divergent input, should be shared with the HTD along with the information about the final PICO(s) in a timely manner.	
Roche	7	107-108/1.3	"…the assessment scope should be inclusive and reflect the MS needs." Suggestion for rewording: *"...the assessment scope should be inclusive and reflective of the MS policy driven-PICOs that is reflective of the current treatment landscape within their country"* This would be more in line with the wording of the regulation that speaks in Art. 8 (6) of "The assessment scope shall be inclusive and reflect Member States' needs in terms of parameters and of the information, data, analysis and other evidence (...)".	
Roche	7	112-113/1.3	*"To minimise the number of PICO(s), the assessor and co-assessor consolidate the PICO(s) as much as possible (Section 3.2)."* There should be a clear set of criteria which can be applied for this minimization and parameters should be used to set a limit to the number of PICO(s) defined for a certain JCA.	
Matias Olsen, EUCOPE	7	109-115	The workload for the EU HTA dossier heavily depends on the PICO schemes defined by the Member States and consolidated by the assessor and co-assessor. As different PICO schemes or changes within a PICO scheme (and this can also mean differing operationalisation of endpoints) can mean substantial changes for the analyses/dossier, clear and reliable timelines for the decision on the final PICO schemes are required for the dossier preparation by the HTD.	
Mihai Rotaru -	7	104-108	As per introductory comment above, EFPIA proposes that HTD present a draft PICO in a	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
EFPIA			letter of notification to the Coordination Group, as a supportive document for undertaking the assessment. This would be reviewed by the assessor and co-assessor and inform the survey sent to MS. Importantly, in proposing this, EFPIA is looking beyond the EUnetHTA21 phase of JCA implementation.	
Silke Walleser Autiero Medtronic	7	108-110	When seeking input from member states, we suggest that this be extended to input not just on the PICO but also (in a prior step) on the policy question the member state is aiming to address. This would ensure the JCA meets the needs of member states and is initiated at the right time.	
EFSPI	7	118-120	Please add links / references to the articles 8-10 (for ease and clarity)	
Paolo Morgese - ARM	7	111-113	The approach taken to "minimise the number of PICOs" does not look appropriate as it allows a large number of PICOs and is likely to result in a submission process that is not feasible and cumbersome for HTDs.	
Mihai Rotaru - EFPIA	7	91-92	Replace "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" with "[…] the scope of the assessment should not be limited by the available studies and also be informed by the common requirements of the health care systems of the MS where these differ materially from the key trial datasets.	
Matias Olsen, EUCOPE	7	104-105	Please specify *„well in advance*". In general, specific timelines are not mentioned in this guideline. Open questions include: •Are there specific timepoints that indicate whether the HTD can request the initialisation of the scoping process? •When exactly does the scoping process start? At which timepoint is the HTD informed about the result of the scoping process?	
James Ryan, AZ	7	105-106	It will be critical that the scoping exercise is performed as early as possible, allowing sufficient time for the HTD to prepare a high-quality submission. Based on the current	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			additive approach, we recommend that the scope needs to be finalised at least 6 months prior to HTD submission. Early and ongoing engagement with the HTD during this process will be important to ensure a timely and high-quality submission.	
EFSPI	7	107-108	Current wording: "…the assessment scope should be inclusive and reflect the MS needs." Recommended rewording: "scope should be inclusive and reflective of the MS policy driven-PICOs that is reflective of the current treatment landscape within their country"	
EFSPI	7	114-115	The guideline does not specify the date upon which the output of the scoping process is communicated to the HTD. This should be early enough, ideally at day -160 but not later than day -100. Moreover, at the same time point the HTD should receive the information which parts of national PICOs are not reflected by the consolidated PICOs so that the HTD can prepare early enough for evidence synthesis for national submissions.	
EFSPI	7	Figure 1-1	Definition of "Data" submitted by HTD. In reality, HTDs will submit "information" rather than "data" per se, where "data" could imply datasets that would be re-analyzed by a third party. It may be helpful to define what is meant by "data" here, and ensure consistency across the document	
James Ryan, AZ	7	101	Figure 1-1 would benefit from incorporating the scope of the Regulation to ensure appropriate translation of policy questions into the PICOs are considered and the framework is fit for purpose.	
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)	7	105	Comment: In view of the tight time constraints under the EU-HTA regulation and especially during EUnetHTA 21, precise deadlines are needed to create reliability and trust for all stakeholders. Imprecise time specifications could lead to delays with possibly serious effects on the further tight project schedule. We recommend to set the deadline periods precisely. Suggestion for rewording: *"[…] according to the timeframe for the JCA and no later than XXX days prior to dossier submission deadline."*	
Silke Walleser Autiero	7, 10	105, Figure 3-1	It is noted that scoping will take place well in advance of the JCA, yet the current process outlined does not take this into account. Consideration should be given to providing clear	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Medtronic			selection criteria for HTA and clear and specific evidence requirements, to ensure some predictability in the process for HTD and clinical evidence investments.	
MTE	7	105	**Scoping well in advance of the JCA**. This will indeed be a critical factor of success. A special provision will need to be developed as the **medical technology** that will pass through a JCA will only be known once **selected** by the EC based upon an interest of the member states and fulfilling selection criteria defined in the regulation. (Art.7, 4). Hereby will the specificity on evidence generation (See preample 37) be important to be taken into consideration. The both for JCA in general and for a possible focus on Early JCA as developed in the JCA for high risk medical devices by EUNETHTA 21. We look forward to specific proposal and guidance	
MTE	7	108	**Reflect member states needs.** As well described in the introduction it will be important to align the PICO questions to the policy question(s) and to the unmet medical need of the patients (MS needs). As for medical technologies Member States seek to answer different policy question we propose that the specific policy question a MS seeks to answer is part of the input MS provide. Hereby then also specifying the timepoint when they seek to address this policy question to obtain an overview also in the dimension of time. Hereby a specific information might be towards the interest of obtaining an early JCA enabling to accelerate the introduction and accessibility of innovation	
Mihai Rotaru - EFPIA	7	109	See introductory comment above, and EFPIA's recommendation for a revised PICO development process. This revised process elevates the role of the assessor and co-assessor in developing a draft PICO, which in turn should assist in planning for the technical and resource requirements of the assessment proper; it also highlights the needs for patient and HCP engagement at the EU level rather than limiting this to the Member State level. Importantly, such a process should improve the effectiveness, accuracy and timeliness of the PICO Member State survey process by anchoring it in a draft PICO to which they can respond to.	
BIOTRONIK SE & Co. KG	7 11 12	109ff 203ff 3.2	The suggestion of an unlimited number of possible comparators for which the HTD must develop evidence seems unreasonable given the breadth of EU healthcare systems and practices within. For example, possible comparators for implanted cardiac monitors (ICMs) exceed 5 just in type (pulse palpation, holter ECG, in clinic ECG of various frequency, cardiac wearables, other ICMs and ICMs with and without remote monitoring). This is not accounting for different device types and software version utilised, leading to a potential	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			exponential increase in comparators which could be requested, depending on varying standards of care. HTDs cannot be requested to raise this variety of evidence, as it is likely to lead to overall poor data quality not allowing for reasonable assessment and unnecessarily large studies, exposing patients to inferior or experimental care. We suggest an addition of the following sentence at the end of section 3.2: The assessor / co-assessor will limit the PICO(s) to a reasonable number, allowing for the assessment of added benefit vs pan-EU most prevalent standards of care focusing on most current and up-to-date guideline-led practices.	
James Ryan, AZ	7	110	To help ensure timely preparation for complimentary analyses, including both clinical and economic at a Member State level, as well as supporting the principle of transparency, the Member State PICOs should be shared with the HTD.	
MTE	7	112	**Consolidation of the number of PICO.** The consolidation should not be limited to the convergence exercise of MS PICO requests, but the guidelines should better characterize how the final PICO will be set and what minimum criteria will be considered to have the request of national PICO to be part of the consolidate PICO. This exercise will be of critical importance, whereby an involvement of the HTD will be of high value . This given their knowledge related to the clinical data available and especially for the targeted medical devices the confounding factors by the MS specific healthcare delivery processes. A further consolidation should also be discussed in dialogue with HTACG, often holder of (indirect) comparative data to also confirm the further ability of use of the JCA and/or additional analysis to be expected at national level.	
Mihai Rotaru - EFPIA	7	114	In addition to the final assessment scope provided to the HTD, EFPIA recommends that divergent recommendations and input gathered during the PICO survey (the responses to the survey) by the countries should be made visible to the HTD to allow to prepare for potential complimentary (unavoidable) request and submissions (providing predictability both for HTD and MS).	
Tanja Podkonjak – Takeda Pharmaceuticals International AG	7	114	In addition to the final EU Joint Clinical Assessment scope provided to the HTD, Takeda recommends that completed PICO surveys by MS or MS input gathered during the PICO survey stage be made available to the HTD. This would enable the HTP to prepare for potential complimentary request and submissions at national level, improving efficiency of the HTA process and ideally faster funding decisions.	
Prof. Matthias	7	115	Comment:	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)			According to HTA Regulation (EU) 2021/2282 Article 8 (6) sentence 2 "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." Hence, the final assessment scope provided to the HTD shall enable the submission of a dossier fully meeting the needs of every MS. An assessment scope which enables the submission of a dossier "in principle" meeting the needs of every member state would not be sufficient. We recommend to delete "in principle" from the sentence. Suggestion for rewording: *"[..] enables the submission of a dossier ~~in principle~~ meeting the needs of every MS."*	
James Ryan, AZ	7	115	"enables the submission of a dossier in principle meeting the needs of every MS" Please see previous comments regarding Regulation use of complementary clinical analyses as well as concerns around redundant and disproportionate added analyses	
James Ryan, AZ	7	117	Point 15 in the Introduction to the Regulation is also important, providing context in the interpretation of the Articles.	
EFSPI	7	127	Refers to "study" and should refer to study(ies) to allow that there may be more than one relevant study in scope.	
Dr. Thomas Ecker, Ecker + Ecker GmbH	7	104–105	**Statement in guideline:** "*The scoping process is initiated by the Joint Clinical Assessment (JCA) secretariat according to the timeframe for, and well in advance of, the JCA."* **Comment:** Please specify „*well in advance*". In general, specific timelines are not mentioned in this guideline. Open questions include: • Are there specific timepoints that indicate whether the HTD can request the initialization of the scoping process? • When exactly does the scoping process start? • At which timepoint is the HTD informed about the result of the scoping process?	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			We suggest that the scoping process starts as soon as the marketing authorisation application (MAA) has been confirmed. Similar to Joint Action 3, the prospective marketing authorization holder (pMAH) should then have to opportunity to hand in a "letter of intent" as soon as the marketing authorization application has been submitted. In this document, the pMAH should provide insights into the expected timelines as well as the proposed indication. Moreover, this letter should include a proposal for the assessment scope comprising the appropriate PICO scheme from the HTD's point of view.	
James Ryan, AZ	8	141-146	We would recommend that the HTD has the opportunity to provide a proposed PICO that should be shared with the Member States when the survey is sent out.	
James Ryan, AZ	8	135-139	The assessor and co-assessor should also have an active role ensuring these factors are also considered in the final consolidated scope.	
James Ryan, AZ	8	147 - 151	The assessor should only share the fact that a JSC has taken place. Given the potential commercially sensitivity of the JCS, the content of it, including recommendations, should only be shared with Member States after consent of the HTD.	
Tanja Podkonjak – Takeda Pharmaceuticals International AG	8	126-128	Section 2 Scope and Objective of the Guideline states: "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." However, the Scoping Guideline does not provide guidance on what is expected from HTDs in the situation that re-analyses need to be conducted. The Scoping Guideline in Section 6 lines 404-418 only mentions that analyses deviating from the original study plan should be clearly mentioned. It is respectfully requested that either: 1. The Scoping Guideline explicitly states what information is expected from HTDs should re-analyses be needed, or 2. That the Scoping Guideline in Section 6 explicitly states that guidance on what information is expected from HTDs in the situation that re-analyses are needed will form part of the JCA template and be communicated in a future guideline.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			This can help standardize the information provided by HTDs in the submission dossiers and will work to ensure that the HTDs will include the information that assessors of the submission dossier expect.	
Mihai Rotaru - EFPIA	8	120	The consequence of non-compliance from Article 10 of the regulation needs further expansion in the scoping process and methodology, in the context of 'feasibility'. If analyses requested by MS are not feasible due to complex or incomplete evidence networks, then some evidence requested may not be possible to generate. Since the evidence requested directly derives from the Scope, this feasibility issue needs to be addressed in the context of this consultation.	
Mihai Rotaru - EFPIA	8	122	EFPIA proposes that the guideline should clearly indicate its applicability. EFPIA understands that the guideline is intended to inform the scoping process for assessments under the future HTAR (and not only for EUnetHTA21 purposes). As such, EFPIA comments throughout this document are made towards that objective. With implementation of the HTAR in view, the guideline should also detail how the scoping process will fit into the JCA process, in a workable and sustainable manner for all stakeholders. We therefore recommend the document be expanded to present the scoping process within the timeline of the broader Joint Clinical Assessment (JCA) process; from initiation, through scoping to dossier submission and final JCA report publication.	
Sebastian Werner vfa	9 19	141-146/ 3.1.2 349-357/ 3.3	The guideline does not include a **meaningful involvement of HTD** in the scoping process or in the validation of the PICO. A F2F or online scoping meeting with the HTD should be included to allow clarifying questions, to explain its position and data availability and discuss the range of appropriate methodological analyses to assess the parameters included in the assessment scope. The implementation of a scoping meeting with the HTD would be consistent with the past practice in EUnetHTA assessments and current practice in Germany as part of dossier consultations. In both instances the scoping meeting revealed large benefits for the HTD and the process in general. Hence, the scoping meeting with the HTD has proven very useful in the past and must not be abolished. The implementation of a scoping meeting is also consistent with the regulatory framework of	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			the HTAR, that establishes a similar involvement of HTD, patients and clinical experts in the scoping process [Article 8(6)]. Hence, the JCA CSCQ Meeting that involves patients and clinical experts for PICO validation could similarly involve the HTD. However, a separate HTD scoping meeting ahead of this procedural step would be as beneficial.	
Sebastian Werner vfa	9	148 / 3.1.2	The guideline displays a disconnect of the **JSC recommendations** and the scoping process. The authors highlight that JSC recommendations might no longer be applicable because of changes in the underlying conditions, while "the PICO for the assessment should be generated under the conditions existing at the time of the survey". The guideline lacks a description of the importance of the JSC for JCA and the European HTA. The JSC is critical for the HTD to enable evidence generation according to requirements of the European HTA bodies and thus is essential for predictability, feasibility, and a well working EU HTA. The guideline should therefore highlight the importance of a **reliable use of the JSC in the scoping process**. Changes of the JSC recommendations should be carefully considered and well justified. The availability of joint scientific consultations must be sufficient to meet demand and be equipped with adequate capacities.	
Sebastian Werner vfa	9	138-139/3.1.1	The guideline states that MS are encouraged to **involve local patients and clinical experts** during the PICO survey to ensure that their inputs cover all their needs for national evaluation. It should be clarified how patients and clinical experts should be involved. The vfa recommends to strongly encourage the MS to involve local patients and clinical experts during the PICO survey.	
Edwards Lifesciences	9	138/ Section 3.1.1 Objective of the PICO survey	"MS are encouraged to involve local patients and clinical experts to ensure that their inputs cover all their needs for a national evaluation" should be changed to (additional text in bold): "MS ~~are encouraged to~~ **should** involve local patients and clinical experts to ensure that their inputs cover all their needs for a national evaluation"	
Edwards Lifesciences	9	156/ Section 3.1.3 Format of the PICO survey	We consider the 2 week timeline to be too short and unrealistic to gather the information and respond to the survey by the MS. We suggest to reword as follows (additional text in bold): "MS are expected to answer within **at least 4 calendar weeks** ~~approximately 2 weeks~~."	
Edwards	9	157-158/	We believe that successful scoping requires a **smart, proactive and transparent**	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Lifesciences		Section 3.1.3 Format of the PICO survey	**prioritization of technologies to be assessed based on: unmet healthcare need, transparent assessment** or disinvestment criteria, avoiding potential duplications and evaluation of obsolete technologies. How will this scoping guideline ensure that all MS respond to the survey? and should there be a minimum number of surveys received to continue the process?	
GSK	9	General	Two alternatives to a smaller set of EU adhoc-analyses most countries can agree on: (1) Either form a cluster-based approach for MSs with comparable HTA needs, (2) form a set HTA modules (PRO, Subgroups, etc.) which particular MS borrow from via multiple inheritance (such as in C++) and possibly slightly modify to suit their needs.	
Norbert Gerbsch for IGES Institut GmbH and HealthEcon AG	9	141/142 / 3.1.2	"The questionnaire for the PICO survey considers 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)…" **Comment:** Art. 8 (6) of REGULATION (EU) 2021/2282 does not define the information to be provided by HTD in detail: „The scoping process shall also take into account information provided by the health technology developer…". Therefore type and depth of information should be specified. **Suggestion:** Add: „The HTD is requested to provide information on the claimed indication, a description of the disease and the medical need as well as the studies considered relevant (PICO, design, etc.)"	
Norbert Gerbsch for IGES Institut GmbH and HealthEcon AG	9	147 / 3.1.2	„The MS will be made aware of any Joint Scientific Consultation (JSC) that might have taken place for the medicinal product or MD under discussion.". **Comment:** Apart from not being binding on EU level, MS should nevertheless also be aware of national scientific consultations to avoid double work and to consider relevant input for the assessment. **Suggestion:** Change to „The MS will be made aware of any Joint Scientific Consultation (JSC) or national Scientific Consultations that might have taken place for the medicinal product or MD under discussion."	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Norbert Gerbsch for IGES Institut GmbH and HealthEcon AG	9	148+ / 3.1.2	**Comment:** As mentioned in the guidance document the JSC recommendations might no longer be applicable due to different reasons. Therefore, the HTD as well as the assessors are compelled to keep track regarding any changes that might have an impact on the PICO(s). However, occuring changes might be perceived differently by the HTD and EUnetHTA21 regarding potential changes to the PICO(s). Since the decisions from EUnetHTA21 regarding PICO(s) have a major impact on data presentation in the JCA, EUnetHTA21 should proactively inform the HTD if any changes lead to PICO(s) differing from JSC to ensure compliant data presentation. **Suggestion:** Add to line 151: "The HTD will be informed at the earliest possible time of any changes in the underlying conditions that in consequence lead to PICO(s) differing between JSC and JCA. If necessary, appropriate measures will be taken to provide for sufficient time for neccessary re-analysis within the legally binding timeframe."	
Norbert Gerbsch for IGES Institut GmbH and HealthEcon AG	9	165 / 3.1.4	**Comment:** Art. 8 (7) of REGULATION (EU) 2021/2282 requires the Coordination Group to inform the Commission of the (final) assessment scope of the JCA while Art. 10 (1) requires the Commission to inform the HTD. As this obligation relates to the final PICO, there is no reason not to involve the HTD in the validation phase during which PICOs are in a preliminary state. **Suggestion:** „During the validation process sufficient time will be granted to the HTD to comment on the preliminary PICO schemes and to request clarification on inexplicit aspects."	
Roche	9	138-139/3.1.1	The selection of comparators by the MS for the survey should follow a structured approach ensuring a final list of comparators that is reasonable and concise. The priority should be given to established licensed medicines with published robust clinical data, followed by those recommended in up to date European clinical guidelines.	
Roche	9	141-146/3.1.2	There should be a template for all HTDs to use for the letter of intent. In addition to the information on the intervention and the intended use according to the regulatory submission, the HTD should also have the opportunity to provide a	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			proposal for the PICO. It seems all key stakeholders are invited to contribute to the PICO discussion, apart from the HTD. This does not seem expedient. The PICO sets the basis and the framework for the later JCA. This affects the rights of the HTD and therefore the HTD should also be consulted and given the opportunity to comment.	
Roche	9	147-151/3.1.2	A comprehensive PICO across the EU HTA should already be defined at the JSC stage. Discussions on the PICO should be part of JSC, i.e. the PICO survey should happen at different development stages: start at the JSC for clinical development decisions and update before the JCA. The HTD should also be consulted and given the opportunity to comment both at the JSC and at the JCA stage. All discussions and revisions leading to the finalisation of the PICOs at the time of the JCA should be shared with the HTD.	
Roche	9	144-146/3.1.2	*"This information is to be provided by the HTD upon request, before the beginning of the scoping process, in a letter of intent (for EUnetHTA 21 context, to the EUnetHTA secretariat)"* Needs clarification, either this information is expected to be shared proactively through a letter of intent or reactively upon request. Both are not possible. In addition does the text of the law not restrict the information provided by the HTD. The HTD must be allowed to provide relevant information.	
Roche	9	165-166/3.1.4	Suggestion for rewording: *MS are asked to limit their requests to the extent necessary for their national decision making. The selection of comparators by the MS should follow a structured approach ensuring a final list of comparators that is reasonable and concise. The priority should be given to established licensed medicines with published robust clinical data, followed by those recommended in*	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			European clinical guidelines.	
EFSPI	9	138-139/3.1.1	The description should also mention that member states should complete their survey based on evidence, utilizing the most current guidelines available, and are restricted to the most representative treatments (e.g. true standard of care, reflecting real-world practice).	
Matias Olsen, EUCOPE	9	135-139	Is the feedback of the PICO survey provided from Member States to the assessor/co-assessor made public? Can the decision-making process/rationale on how the assessors defined the final PICO schemes be made public?	
Matias Olsen, EUCOPE	9	147-151	•Can the results from the JSC be applied to the final PICO scheme? •Are all Member States involved in defining the PICO scheme within the framework of JSC? Discrepancies between the PICO scheme defined as part of the JSC and the final PICO scheme affect transparency and predictability of the whole procedure. Comparators defined within the process of JSC should always be included in final PICO schemes. The Assessors should also be made aware of national scientific consultations.	
Liebenhoff, BAH	9	141 - 144	"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)]." As in the quoted Article 8 (6) the information includes beside information on the intervention and the indication also the comparator and the health outcomes. It is crucial for the technology developer to submit arguments for the whole PICO-scheme that is relevant from his point of view. Therefore, we propose the following amendment: "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	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			intended use according to the conformity assessment [in the case of medical devices (MD)], as well as information about the comparator(s) and health outcomes."	
Matias Olsen, EUCOPE	9	142-145	The HTD should have the opportunity to submit a PICO suggestion based on available evidence. Replace: "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…" With: "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: **the HTD is to provide information on the claimed indication, a short description of the disease and the medical need as well as the studies considered relevant (PICO, design etc.)** and the indication for which the HTD applied in the regulatory submission dossier…"	
Paolo Morgese - ARM	9	148-151	It is not clear when the PICO survey will be done and how much time the HTAD will have to prepare the filing. The Scoping Process in terms of timelines and selection of PICOs should respond to reasonable standards of feasibility. Given the complexity of ATMPs, and the challenges in generating evidence in rare and ultra-rare indications, JSC is a key exercise in identifying PICOs and setting up a compelling evidence generation plan. JSC should play a much more important role than described in these draft guidelines. JSC should be part of a continuum of interactions between the EU HTA instances and HTAD including: JSC, JCA, post-launch evidence generation and eventual re-assessments.	
M. Ermisch – GKV-Spitzenverband	9	164-166	These lines should be deleted. They indicate that MS would ask for information that is not necessary, which would be in contradiction to the legal framework of appropriateness that are binding for public institutions.	
Liebenhoff, BAH	9	144 -146	"This information is to be provided by the HTD upon request, before the beginning of the scoping process, in a letter of intent (for EUnetHTA 21 context, to the EUnetHTA secretariat) and this information will be made available to the MS." With reference to Art. 8 (6): The assessment scope shall be inclusive and reflect Member States' needs in terms of parameters and of the information, data, analysis and other	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			evidence to be submitted by the health technology developer. For that "upon request" has to be deleted. Therefore, we propose the following amendment: "This information is to be provided by the HTD, before the beginning of the scoping process, in a letter of intent (for EUnetHTA 21 context, to the EUnetHTA secretariat) and this information will be made available to the MS."	
Matias Olsen, EUCOPE	9	130-131, 144-145	Are the "*request for assessment by the HTD*" (p. 9, line 130–131) and the "*letter of intent*" (p. 9, line 144–145) identical or two separate documents?	
Matias Olsen, EUCOPE	9	157-159	The consequences of not submitting a PICO scheme are not specified. May a Member State that has not submitted a PICO scheme still request evidence at the national level? Has this aspect been considered in the EU regulation?	
James Ryan, AZ	9	161-163	Recommend to add (in bold) "It is the responsibility of the MS to define the PICO parameters according to their national legal and procedural requirements**, as well as the clinical scope of the EU HTA Regulation.**"	
James Ryan, AZ	9	164-166	We agree with the statement about the impact of requests. However, a MS will not be aware if their request will increase the scope as the assessors will not provide an initial PICO. Furthermore, this principle around impact on workload should also be considered at the consolidation point so as to avoid both disproportionate analyses (those that affect a relatively small number of EU patients or Member States) and redundant analyses undertaken due to the proposed additive nature (as described earlier).	
EFSPI	9	164-166	To ensure operational feasibility of PICOs, it is recommended that member states are encouraged to proactively consider exchangeability of comparators within the class of treatments where applicable. For example, a member state may ideally want treatment A as a comparator but be willing to accept treatment B from the same class. In that case, the member state should be	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			encouraged to specify (treatment A OR treatment B) and not just (treatment A).	
Tanja Podkonjak – Takeda Pharmaceuticals International AG	Page 9	135-137	The Scoping Guideline states: "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." However, Section 3.1 The PICO survey and APPENDIX 1 PICO SURVEY FORM only reference the population, intervention, comparators, outcomes, additional information without making any mention to analysis requested. Furthermore, Section 4 INFORMATION FOR THE HTD states that the HTD will be informed of the scope and the PICO(s) which as mentioned before do not reference analysis/analyses. Takeda respectfully requests that the word **analysis** be removed from the text in Page 9 lines 135-137, so it is clear that in the PICO survey, MS will only be asked for input on the research question(s) and data requested.	X
Mihai Rotaru - EFPIA	9	152-153	As indicated previously, not having the assessors involved in drafting the initial PICO seems inefficient and counter to the concept of an EU JCA. As per the introductory comment, we recommend that the HTD puts forward the initial PICO for review with the assessors who in turn develop a draft PICO to anchor the Member State survey	
M. Ermisch – GKV-Spitzenverband	9	155-156	This timeline is rather short and does not fit current procedures in Germany, especially if no JSC was performed for the HT or the conditions taken into account during the JSC are no longer valid. Even if the current procedures in Germany are changed, decision-making processes will need 4 weeks at least. This is true for PICOs for medicinal products and especially for medical devices. It is uncertain, whether adapting national processes for medicinal products such as deciding upon the national PICO at the time of application for marketing authorisation is sufficient, as changes from the indication applied for to the indication grated might affect the population and comparators. Please refer to comments on the flowchart on page 10 additionally.	
Matias Olsen, EUCOPE	9	130-131	Will a "request for assessment by the HTD" be necessary, once EU-HTA is mandatory?	
Matias Olsen, EUCOPE	9	130-131	Does the letter of intent, as indicated here, have to be submitted only upon request?	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Matias Olsen, EUCOPE	9	130 - 131	Please specify the timelines related to the scoping process: •When should the request for the assessment by the HTD be submitted? •When exactly will the consolidated final PICO be communicated to the HTD? •How does EUnetHTA21 know that "Day -45" prior to CHMP opinion is reached? How do regulatory clock stops (e. g. in response to Day 180 List of Questions) impact the EU-HTA timeline? Moreover, HTD should be included in the scoping process. Scoping meetings with HTD should be incorporated to discuss the PICO scheme and related open issues. Overall, the procedure must ensure the broad involvement of HTD. A mandatory duration for consolidation of PICO scheme should be added, as is the case in for example the AMNOG procedure in Germany. Add: "In EUnetHTA 21, the scoping process starts with the submission of a request for assessment by the HTD and ends when the consolidated final PICO is communicated to the HTD. **The PICO scheme must be communicated to HTD developer no later than x weeks after application of the HTD (letter of intent)**"	
GSK	9	155-156	Is that survey one-off or repeated at some interval like every 1 or 2 years?	
Silke Walleser Autiero Medtronic	9	152-153 161-162	As noted above, a national health technology assessment may not be required in many member states at the time or shortly after CE-mark, and thus member states might not yet have the insights enabling them to formulate relevant PICO questions (adapted to their specific national or regional setting). Thus, the creation of PICO purely based on member states' input might not be practical for many member states. Evaluations not relevant for downstream selection in member states should be a factor to consider when soliciting input. We recommend to also involve the respective HTD in the PICO development process (see also comment to 3.1.2)	
Silke Walleser Autiero Medtronic	9	155 - 156	Will member states be actively alerted of the PICO survey or do they need to monitor?	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Silke Walleser Autiero Medtronic	9	157-158	Could it be clarified what is meant by "outside of the remit" in the context of member states' need to input to the PICO? Member states should have the option whether to provide input during the PICO phase or not, taking into account different member states' need for and capability to input to JCA in particular to early JCA.	
James Ryan, AZ	9	152-153	we propose that the HTD should submit a PICO that can be shared at the start of the survey with the MS. If this does not occur, then the assessors should consider providing a proposed PICO. One of the Regulation aims is to avoid duplication. It is feasible that the assessors could issue a PICO based on European clinical guidelines for the most relevant best alternative comparator, EMA assessed endpoints, and sub-population based on the label vs overall trial population, as well as pre-specified biologically plausible sub-groups in the clinical trial. This would provide additional information for Member States, avoid duplication, and help enable timely return of the survey.	
EFSPI	9	138-139	There is mention of "local patients" and "clinical experts". It would be valuable to also consider independent statisticians and academic groups	
EFSPI	9	150-151	Current wording: "The PICO for the assessment should be generated under the conditions existing at the time of the survey". However, evidence and conditions can change after the survey. There should be a process to describe if/how PICOs may updated considering e.g. new data and preliminary feedback from EMA regulatory review or changes in the member state health technology landscape, and how updates will be communicated to the HTD.	
Tanja Podkonjak – Takeda Pharmaceuticals International AG	Page 9	150-151	The proposed Scoping Guideline currently states: "The PICO for the assessment should be generated under the conditions existing at the time of the survey." Takeda requests further clarification on the implications of this statement to potential changes in the treatment landscape which may occur during the JCA process itself. In specific, if a new technology receives EMA approval in the target indication while the intervention in question is undergoing a JCA, how will this impact the JCA? It is our	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			understanding that once the JCA scope is set, further changes during the JCA process will not impact the scope nor will the PICO change. We request the scoping guideline should address this situation and explicitly state the impact of post-scoping changes on the JCA requirements so that it is transparent that no changes would occur in the PICO(s) while the HTDs are preparing the submission dossier. Alternatively, the Scoping Guideline should be explicit about which situations a change in the PICO(s) could occur once it has been finalised and communicated to the HTDs.	
Tanja Podkonjak – Takeda Pharmaceuticals International AG	Page 9	155-156	Takeda requests the Scoping Guideline clarifies what happens if a MS does not participate in the PICO survey or is unable to complete the survey in the suggest 2-week period. In this event, we request the guideline make it clear that after the PICO(s) has been finalised and communicated to the HTD, no changes will be made as a consequence of a MS submitting the survey late. As previously noted, Takeda is concerned that the proposed 2-week turn around period for the PICO survey to the MS is too short. Given current national HTA scoping processes, we are concerned about the feasibility of this timeline for MS to complete the survey and include patient and clinical input and suggest this be extended, in line with Takeda's comments on the timelines of the scoping process provided in the General comments section.	
Tanja Podkonjak – Takeda Pharmaceuticals International AG	9	162-163	The Scoping Guideline currently states: "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 1." Takeda recommends that the PICO(s) survey submitted by MS and the consolidated PICO(s) at the EU level should also include the rationale for the definition of the population, intervention, comparator(s), and outcome(s), and additional information and that this information be shared with key stakeholders, including the HTD. This will allow for a transparency in the definition of the decision problem(s)/research question(s). Takeda recommends the PICO table in Appendix 1 include a column for the rationale of the component of each PICO submitted by MS.	X

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Silke Walleser Autiero Medtronic	9	3.1.1 3.1.2	HTD needs to inform on the intended use according to the conformity assessment in case of medical devices. This might not be the only meaningful information for definition of PICO relevant for HTA because the policy question to be addressed might focus on a narrower indication than addressed in the CE certificate/Intended Use documents. Also, there is the possibility that indications change after expert panel review. We therefore strongly recommend to follow HTA best practice processes in this regard and to involve HTD as key stakeholders in the scoping process, to ensure all critical information about the technology, its intended use, and clinical outcomes, are considered appropriately. Also, by including HTD, valuable information on regulatory details and the link between indications and clinical trial design can be obtained.	
Silke Walleser Autiero Medtronic	9	3.1.2	For the initiation of the scoping process, it is important to note that the coordination group, according to the regulation, has an annual workplan of JCAs for medical devices, and that a designated subgroup (of the coordination group) shall initiate the scoping process (Article 8 (6)). This raises the question of the timing of initiation of the scoping (and assessment process), that should be clarified. It is not clear how an initiation of the JCA in parallel to the CE-marking is feasible, and why the development of the PICO needs to be commenced as per the intended use in the submission (and not in accordance with the final labelling).	
AIM – International Association of Mutual Benefit Societies	9	3.1.2 Available data for PICO survey	This information is to be provided by the health technology developer (HTD) ~~upon request~~, before the beginning of the scoping process, in a letter of intent (for EUnetHTA 21 context, to the EUnetHTA secretariat) and this information will be made available to the MS.	x
AIM – International Association of Mutual Benefit Societies	9	3.1.3. Format of the PICO survey	Include what consequences are for not responding or mention that consequences still need to be defined	
Dr. Thomas Ecker, Ecker + Ecker GmbH	9	Section 3.1.4	**Comment:** Will member states have to provide detailed information on how the resulting PICO scheme was developed? Will this information be shared with the HTD?	
Norbert Gerbsch for	9	130 / 3	**Comment:** According to section 3 "In EUnetHTA 21 the scoping process starts with submission of a request for assessment by the HTD…"	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
IGES Institut GmbH and HealthEcon AG			The fact, that starting the process is attributed to the HTD by initiating the scoping process is welcomed. It is however unclear what formal requirements have to be fulfilled to submit a request: Is this an informal letter or have prespecified documents or data to be submitted? If yes: Which? It seems that information according to Art. 8 (6) of REGULATION (EU) 2021/2282 is to be provided by the HTD only upon request (see line 145). **Suggestion:** Add "A sample form for the submission of a request for assessement will be provided by EUnetHTA21"	
Mihai Rotaru - EFPIA	9	133	EFPIA considers that the model proposed by the scoping process is more of an amalgamation of country PICOs, rather than a streamlining of evidence requirements (one of the overarching objectives of the HTAR). As per the introductory comment, EFPIA proposes the adoption of a genuinely ***European*** perspective for the JCA, one that focusses on what is common to the health systems of the MS, rather than seeking to meet the individual and sometimes divergent needs of each. We believe that this is fully consistent with the intention and sprit of the HTAR. The proposed methodology for the PICO development risks, for some products, introducing unnecessary analytical complexity as well as corresponding evidentiary uncertainty. This is especially the case where local and historical variations in clinical practice that exist across the MS translate into a multiplicity of requests for analyses of country specific sub-populations that are not pre-specified in the trial data and for the use of a multitude of comparators that require the adoption of indirect treatment comparisons – the methods for which are not looked upon favorably by all EUnetHTA21 members.	
Tanja Podkonjak – Takeda Pharmaceuticals International AG	9	133	Takeda considers that the model proposed by the scoping process, a simple amalgamation of individual country PICOs, may not achieve a truly pan-European scope and may result in an overly complex JCA scope. This approach may not achieve the streamlining of evidence requirements, which is one of the overarching objectives of the HTAR. An additive or simple amalgamation approach to the JCA scoping process does not address the issue of different scoping methodologies which current exist between MS. In addition,	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			this approach is not founded in previous experience from the EUnetHTA JA3 and thus adds new significant complexity to a new process. Takeda proposes a scoping methodology be applied at an EU level that is representative of the majority of European population and EU clinical practice, but is still pragmatic and guided by the available evidence. With this approach, we recommend the EU JCA scope filter out outlier comparators and sub-populations that are not relevant to the majority of EU patients. We recommend these be considered as complimentary assessments at individual MS levels. We note that under the HTA Regulation, individual MS are still permitted to conduct complimentary analyses should they have specific local needs or comparators which are not used in other MS.	
Mihai Rotaru - EFPIA	9	138	In order to maintain the true value added of an EU assessment, EFPIA recommends that inclusion of patients & HCPs views to inform the assessment scope be done at EU level, as indicated above.	
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)	9	138	Comment: According to HTA Regulation (EU) 2021/2282 Article 8 (6) sentence 4 "the scoping process shall also take into account […] input received from patients, clinical experts and other relevant experts". Input from affected patients and clinical experts for the disease in question is crucial to fully understand and cover the current standard of care and unmet need in an indication. Although not specified whether this input shall be gathered on national and/or EU-level, input from respective patients and clinical experts is needed from all MS since the standard of care and unmet need can differ nationally. Furthermore, it is possible for MS to delegate the task of defining the required PICO parameters to their national HTA bodies, in which payers can make up a large proportion of the voting members (e.g., G-BA in Germany). Hence, including affected patients and clinical experts in the scoping process on the national level could help to ensure that PICO requirements such as the comparator are not selected solely based on economic considerations. In the present draft of the sub-deliverable D4.2 – Scoping Guideline "MS are encouraged to involve local patients and clinical experts to ensure that their inputs cover all their needs for a national evaluation" (page 9, lines 138-9) and "patients and clinical experts are invited to comment on consolidated PICOs" (page 19, lines 354-5). The current wording allows for the possibility that input from patients and clinical experts is not actively sought at either step of the scoping process.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			We recommend rephrasing at least one of the relevant passages, preferably both (cf. comment to page 19, line 354). Suggestion for rewording: *"MS are required to request written statements from local patients and clinical experts in the respective therapeutic field […]"*	
MTE	9	138	**MS are encouraged.** We call for further clarity and clear guidelines on how this is ensure. Also the degree and modality information on HCP, Clinical Staff, patient experienced with the information can be provided by HTD.	
Tuomas Oravilahti, FIMEA	9	140	Information on clinical trials should be included, see our comment for page 6 for details.	
Mihai Rotaru - EFPIA	9	141	EFPIA recommends that the HTD should be enabled to put forwards its views as to which is the most appropriate PICO for the assessment per our introductory comment.	
Tanja Podkonjak – Takeda Pharmaceuticals International AG	9	141	Takeda recommends that the HTD should be enabled to propose the starting or hypothesis PICO for the assessment. We recommend this be done by submitting a 'letter of notification' to the Coordination Group, upon acceptance of EMA submission, outlining the characteristics of the technology as well as the proposed PICO for the assessment.	
M. Ermisch – GKV-Spitzenverband	9	142	Please check the term "intended use" to bring the phrase in line with MDR art 2, No. 12: "intended purpose". This is to be changed throughout the guideline, e.g. in the flowchart on page 10, page 11 lines 175 and 189.	x
Matias Olsen, EUCOPE	9	144	Add: "…in the case of medical devices (MD)] **The HTD furthermore submits a PICO suggestion based on available evidence.**"	
MTE	9	146	**Information on indication.** While the indication is defined as part of the CE marking, we propose that the manufacturer indicates the "indication" for which evidence for a JCA is available. This for the full population as for subgroups for which a sufficient evidence set is available.	
Mihai Rotaru - EFPIA	9	147	EFPIA proposes that the HTD should summarize key areas of advice on the PICO question(s) received in the JSC (if a JSC has been undertaken on the respective technology) in the letter of notification, together with information as to how the advice was implemented in the	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			development & evidence generation plan and how it informs the PICO at the time of the scoping process. The HTD should then also provide information on changes to the landscape since the JSC which may be relevant to the PICO. This information should be considered during the consolidation step of the scoping process. Such an approach would increase the value of JSC as a tool to increase predictability of the HTA requirements in JCA, which is one of the goals of JSC. The guideline lacks a description of the importance of the JSC for European HTA. The guideline should highlight the importance of a reliable use of the JSC for scoping. Changes of the JSC recommendations should be carefully considered and well justified.	
BIOTRONIK SE & Co. KG	9	147ff	It is currently not practice that confidential discussions exploring HTDs evidence generation strategies in regulatory scientific advice meetings be disclosed to HTA assessors, allowing for safe exploration of possible development avenues, which fosters innovation. We ask that this practice be maintained to not bias assessors and member states. We suggest the first two sentences in in the paragraph starting in line 147 be stricken and replaced with: HTA advice given prior to JCA may be disclosed to MS with the explicit caveat, that advice may be outdated. Regulatory advice shall be kept confidential and may only be used for assessment or appraisal by the regulatory body which produced the advice.	
M. Ermisch – GKV-Spitzenverband	9	147	Notably, the scoping is not to be confused with scientific advice given to the developer with the aim of improving clinical trials. Thus, the PICO must not take into account the trials actually performed by the HTD. However, deviations from the advice given within earlier JSC regarding PICO must be justified appropriately by changes in the underlying conditions. Thus, PICO definition in JSC, which is not within the scope of this guideline, must also adhere to the principles laid out in sec. 1.2	
Tanja Podkonjak – Takeda Pharmaceuticals International AG	9	147	As the PICO will likely be a main topic for Joint Scientific Consultations (JSC), where an intervention received JSC, Takeda proposes that the advice received in the JSC form the basis of the JCA scope. Furthermore, any changes in the JCA scope that deviate from the JSC advice should be justified based on evidence of practice changes and/or new drug approval. Takeda proposes that if a JSC has been undertaken on the respective technology, the HTD outline the main outcomes of the JSC in in the proposed 'letter of notification'. The letter of	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			notification should also describe how JSC advice informed the HTD proposed PICO and a description of changes (if any) to the current environment (outcomes, treatment landscape) from the time JSC was received.	
Matias Olsen, EUCOPE	9	151	As already mentioned in the guidance document the JSC recommendations might no longer be applicable due to different reasons. Therefore, the HTD as well as the assessors are compelled to keep track regarding any changes that might have an impact on the PICO(s). However, occurring changes might be perceived differently by the HTD and assessors regarding potential changes to the PICO(s). Since the decisions from the assessors regarding PICO(s) have a major impact on data presentation in the JCA, they should proactively inform the HTD of any such changes to ensure compliant data presentation." Add: "…the conditions existing at the time of the survey. **The HTD will be informed in a timely manner of any changes in the underlying conditions that in consequence lead to modified PICO(s) and will be granted sufficient time for necessary re-analysis.**".	
M. Ermisch – GKV-Spitzenverband	9	152	This is an important issue: The PICO survey must be sent out to the MS without prior consultation of assessor and co-assessor - it is within the duties of the secretariat to ensure that the information provided by the HTD is comprehensive to describe the intervention and the population for which the technology is to be authorised.	
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)	9	155	Comment: Information provided by the HTD and the resulting PICO requirements of the MS are highly confidential until publication of the submission dossier and may also contain personal data. We recommend to include the name of the online platform to be used, which must comply with data protection legislation and confidentiality needs.	
Silke Walleser Autiero Medtronic	9	138-139 and 156	Member states are encouraged to involve patients and clinical experts in the PICO survey. However, they are expected to answer within approximately 2 weeks, which is very short and we question the feasibility of the process within these timelines.	
Vaccines Europe	9	155	The guideline proposal assumes that scoping processes to define PICOs are in place in each of the EU MS and thus each country being able to participate in the survey to define PICOs. For vaccines, National Immunisation Technical Advisory Groups (NITAGs) should be	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			considered to input to this survey as NITAGs are in almost all EU MS involved in the assessment and recommendation for inclusion of a vaccination programme into the national immunisation calendar. However, in a recent analysis, only NITAGs in 7 EU MS were found to have a decision-analytic framework suggesting that currently not all NITAGs in the countries may apply a scoping process before assessment and recommendation. Further, HTD can only themselves submit dossiers in 14 out of 27 EU countries. Thus, during the further development and finalisation of this guideline, in particular from a vaccines point of view, feasibility of such a proposed survey including input from NITAGs should be assessed across EU MS. Reference Laigle et al. 2021 Vaccine market access pathways in the EU27 and the United Kingdom – analysis and recommendations for improvements - ScienceDirect	
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)	9	156	Comment: In view of the tight time constraints under the EU-HTA regulation and especially during EUnetHTA 21, precise deadlines are needed to create reliability and trust for all stakeholders. Imprecise time specifications could lead to delays with possibly serious effects on the further tight project schedule. We recommend to set the deadline periods precisely. Suggestion for rewording: *"[…] within ~~approximately~~ 2 weeks"* (delete "approximately") OR *"[…] within 10 working days."*	
Sallie Latimer, Lumanity	9	Line 156	Please collate MS feedback on whether a 2-week timeframe is adequate for PICO survey completion when they are being encouraged to involve local patients and clinical experts to ensure that their inputs cover all of their needs for a national evaluation.	
James Ryan, AZ	9	156	Two weeks, particularly without any proposed PICO, may not be sufficient for many Member States. The scoping process should start as early as possible to ensure both Member States have sufficient time and the HTD as sufficient time to deliver the submission.	
Anna Lien Espeland, Norwegian Institute of Public Health	9	156	2 weeks is quite short time when MS/HTA bodies need input from clinicians and patients. Please state if and when the MS/HTA bodies will be notified in advance that the PICO survey is coming up, so they can plan.	
MTE	9	156	**PICO Survey.** We expect a 2 week period to answer the PICO survey very ambitious. it	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			is unclear how will the guideline secure that enough feedback is received from the MS for this survey and in the very short timeframe?	
EFSPI	9	157	Current wording: "all MS are supposed to participate.." Suggested rewording: "all MS should participate.."	
Mihai Rotaru - EFPIA	9	158	Please clarify what would render an assessment "except those for which the specific assessment is outside of their remit." Consider clarification in a footnote.	X
EFSPI	9	158	Current wording:"except those for which the specific assessment is outside of their remit" Please clarify where this would apply.	
Tanja Podkonjak – Takeda Pharmaceuticals International AG	9	159	The Scoping Guideline currently states: "To meet the objective of the HTAR, which is an inclusive scope, all MS are supposed to participate in the PICO survey except those for which the specific assessment is **outside of their remit**." Please provide further clarification on what would constitute an assessment being outside of a MS remit.	X
Mihai Rotaru - EFPIA	9	161	Please refer to the revised PICO development process recommended in our introductory comment.	
GSK	9	161	Should PICO parameters population and outcome be discussed as part of estimand framework?	
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)	9	165	Comment: According to HTA Regulation (EU) 2021/2282 Article 8(6) sentence 2 the assessment scope shall „reflect Member States' needs [...] of evidence […] to be submitted by the health technology developer". A demand of evidence which is not essential for the MS would inflate the scope of assessment and thereby increase the workload for all stakeholders and impede focusing on actually needed and valuable information. Hence, this document should clarify that MS are obliged to limit their request for evidence to a necessary extend. We recommend rephrasing the sentence. Suggestion for rewording:	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			„MS are obliged to […]"	
Sallie Latimer, Lumanity	9	Line 165	Noted that "MS are asked to limit their requests to the extent necessary for their national decision-making". This is open to interpretation, and we would request clarity is provided on what MS can reasonably expect to be covered at the European vs national level.	
Mihai Rotaru - EFPIA	9	167	Please refer to the revised PICO development process recommended in our introductory comment.	
Tanja Podkonjak – Takeda Pharmaceuticals International AG	9	167	In line with EFPIA's proposal, Takeda supports the inclusion of the following additional steps in the process chart described on page 10. This will improve efficiency of the scoping process and ensure meaningful contribution from key stakeholders (clinicians, patients and the HTD) as well as the expertise of the assessors: For clarity, the proposed additional steps are: • Step 1: HTD submits a letter of notification to the Coordination Group at EMA acceptance of the regulatory dossier, outlining the characteristics of the technology as well as a proposed PICO for the assessment with rationale, including details of a JSC report if one took place. • Step 2: Assessor/co-assessor, together with patient & clinical experts analyse the HTD proposed PICO and develops a draft PICO to be used as a basis for MS survey – MS to respond and suggest amendments with rationale. If the technology received JSC, the JSC recommendations serve as the base PICO, unless material changes have occurred in EU treatment practice. • Step 3: Assessors to streamline survey responses and propose the final draft PICO, with rationale for the final scope, together with input from EU patient and clinical experts • Step 4: Scoping meeting with HTD and the Coordinating Group led by the assessor and co-assessor to finalise PICO. This scoping meeting would allow the HTD to ask clarifying questions, to explain its position and data availability and discuss the range of appropriate methodological analyses to assess the parameters included in the scope. Step 5: Final assessment scope is communicated to the HTD and will form the basis for the JCA submission dossier. Any divergent input gathered during the PICO survey by MS would	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			be address in local complementary submission. To avoid delays, the PICO survey responses from individual MS should be made visible to the HTD to allow for preparation of any complimentary request and submissions; this will improve predictability both for HTD and MS.	
Dr. Thomas Ecker, Ecker + Ecker GmbH	9	130–131	**Statement in guideline:** "*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.*" **Comment:** Whereas on page 7 (line 104–105) it is stated that the "*scoping process is initiated by the Joint Clinical Assess-ment (JCA) secretariat*", here it is specified that the scoping process starts with a request for assessment by HTD. Could you please define in more detail, how exactly the scoping process is initiated? Moreover, more insight into the specific timelines related to the scoping process are required: • When should the request for the assessment by the HTD be submitted? • When exactly will the consolidated final PICO be communicated to the HTD? • How does EUnetHTA 21 know that "Day -45" prior to CHMP opinion is reached? How do regulatory clock stops (e. g. in response to Day 180 List of Questions) impact the European HTA timeline? Moreover, HTD should be included in the scoping process. Scoping meetings with HTD should be incorporated to discuss the PICO scheme and related open issues. Overall, the procedure must ensure the broad involvement of HTD. Will a "request for assessment by the HTD" be necessary, once European HTA is mandatory?	
Dr. Thomas Ecker, Ecker + Ecker GmbH	9	144–145	**Statement in guideline:** "*This information is to be provided by the HTD upon request, before the beginning of the scoping process, in a letter of intent.*"	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			Comment: Are the "*request for assessment by the HTD*" (p. 9, line 130–131) and the "*letter of intent*" (p. 9, line 144–145) identical or two separate documents? Does the letter of intent, as indicated here, have to be submitted only upon request?	
Dr. Thomas Ecker, Ecker + Ecker GmbH	9	147–151	**Statement in guideline:** *„The MS will be made aware of any Joint Scientific Consultation (JSC) that might have taken place for the medicinal product or MD under discussion. 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*." **Comment:** • Are the member states that participate in the JSC bound by their requested PICO schemes? Discrepancies between the PICO scheme defined as part of the JSC and the final PICO scheme affect transparency and predictability of the whole procedure. Comparators defined within the process of JSC should always be included in final PICO schemes and considered for the assessment. Deviations from the original PICO scheme(s) require medical justification.	
Dr. Thomas Ecker, Ecker + Ecker GmbH	9	157–159	**Statement in guideline:** "*To meet the objective of the HTAR, which is an inclusive scope, all MS are supposed to participate in the PICO survey except those for which the specific assessment is outside of their remit. In that case, this should be indicated as an answer to the survey*." **Comment:**	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			The consequences of not submitting a PICO scheme are not specified. May a member state that has not submitted a PICO scheme still request evidence at the national level?	
EFSPI	9,12,19	131, 215-219, 347	List of outcomes seems to be provided separately from PICOs (population (subpopulations), intervention and comparators). Clarifications should be provided, and this should be reflected accordingly in all sections relevant to the PICO selection process	
M. Ermisch – GKV-Spitzenverband	10		Flowchart section PICO survey: It should be defined, at which day (with regards to days before the start of JCA or day before CHMP opinion) the creation of the PICO survey is foreseen. In addition, according to article 8 (6) the scoping process shall also take into account information provided by the health technology developer and input received from patients, clinical experts and other relevant experts. It seems impossible to integrate national patient representatives and national clinical experts in the determination of a PICO within the given timeframe. Since it cannot be expected that all national representatives are fluent in expert English, the timeframe must also allow for translation from English to the national languages and vice versa. Flowchart section Validation: The guideline lacks sufficient detail how EU patient and EU clinical expert input can be taken into account without repeating decision processes on a national level and without jeopardising the consolidation results. Flowchart – Deadline submission dossier Although it might be beyond the remit of this guideline, it should be mentioned that the target for dossier submission depends from the course of CHMP's evaluation of MAA. A longer clock stop as well as an immediate response can affect the proper timing of JCA, resulting in problems down the line in member-states' procedures. The same is true for accelerated assessments, where scoping and JCA will start very early during CHMP's evaluation of MAA.	
Edwards Lifesciences	10	168-169/ Section 3.1.4 Expected	Figure 3-1 starts with "Pharma" and "Medical Devices" but no IVD. How will the guideline capture the specifics of the different types of medical technologies and be adapted to the nature of the technology and its lifecycle?	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
		inputs to the PICO survey		
Edwards Lifesciences	10	168-169/ Section 3.1.4 Expected inputs to the PICO survey	We believe that the scoping should involve **early, dynamic and active scientific dialogue between all relevant stakeholders**, including HTA bodies, regulators, manufacturers, patients, clinicians and healthcare professionals involved through the care pathway, being all of them experts on the matter. Figure 3-1 PICO Survey – National Patients and Clinical Experts: The scoping guideline should ensure that these experts be validated and published transparently.	
Edwards Lifesciences	10	168-169/ Section 3.1.4 Expected inputs to the PICO survey	We believe that the scoping should involve **early, dynamic and active scientific dialogue between all relevant stakeholders**, including HTA bodies, regulators, health technology developers, patients, clinicians and healthcare professionals involved through the care pathway, being all of them experts on the matter. Figure 3-1 Validation – EU Patients and Clinical Experts: The scoping guideline should ensure that these experts be validated and published transparently.	
Edwards Lifesciences	10	168-169/ Section 3.1.4 Expected inputs to the PICO survey	Figure 3-1: We believe each stage should have a timeline and if delayed a "stop the clock" option be possible. The set timeline should be defined in advance through **early, dynamic and active scientific dialogue between all relevant stakeholders**, including health technology developers. For the sake of transparency and to have an inclusive approach of the key stakeholders, we believe the **HTDs should be involved across the entire process including the PICO definition and the scoping meetings**, as well as the review of the first draft JCA.	
Edwards Lifesciences	10	168-169/ Section 3.1.4 Expected inputs to the PICO survey	Figure 3-1 Unrealistic for the whole process to take 45 days. If each stage is timed realistically, it would be longer than this. We believe the set timeline should be defined in advance through **early, dynamic and active scientific dialogue between all relevant stakeholders**, including health technology developers. For the sake of transparency and to have an inclusive approach of the key stakeholders, we believe **the HTDs should be involved across the entire process and participate during the pre-JCA timeframe : PICO definition and the scoping meetings, align on**	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			the evidence requirements and on the timelines required for the submission of the dossier for JCA. The suggested timelines of 45 calendar days is not realistic and depending on the PICO definitions, or additional evidence requirements, more timelines would be required for the HTD to provide sufficient agreeable evidence set. The above should be facilitated through **early dialogue together with the technology developers** to define the evidence needs, the timelines and the PICO criteria.	
Edwards Lifesciences	10	168-169/ Section 3.1.4 Expected inputs to the PICO survey	Figure 3-1 – Please clarify D45 – D0 – Envisaged date for CHMP opinion – does this mean an unlicensed medicine can enter the process? More specifically for medical devices, it is confusing when the process starts. The process EUnetHTA21 proposes also described in section "3.4 Risk of labelling/CE marking indications change" of this document (also described in the draft deliverable D4.7.1/D4.7.2 – MD framework for high risk MD) suggests that: - technologies identification will start even before the HTD submits for the CE mark - the MD selection and scoping starts even before the conformity assessment report is issued by the notified bodies While we appreciate that "the annual work programme shall set out the joint work to be carried out in the calendar year following its adoption" (per the HTA regulation Article 6), it is unclear to us and concerning how the scoping process will be initiated as early as before the submission for the CE mark certificate by the HTDs, leaving room for many uncertainties and potential delays in the access pathway and risk of duplication at the national level. For the sake of transparency and to have an inclusive approach of the key stakeholders, we believe **the HTDs should be involved across the entire process and participate during:** - **the pre-JCA (PICO definition and the scoping meetings, align on the evidence requirements and on the timelines** required for the submission of the dossier for JCA), - **the JCA** (i.e. dossier submission and review of the first draft JCA, and not only for fact checking of the final JCA report), **the post-JCA timeframe (the use and uptake of the** JCA to inform **timely decision on**	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			reimbursement, funding and use of the technologies).	
GSK	10	169 / Figure 3.1	What is the timeline of the scoping process? When are HTDs communicated to about the full PICOs and what is the time between this communication and the submission deadline of the dossier?	
Norbert Gerbsch for IGES Institut GmbH and HealthEcon AG	10	167-168 / 3.1.4 Figure 3-1	**Comment:** Timelines are missing. PICO survey, consolidation and validation require fixed timelines (e.g. comparable processess such as AMNOG-procedures in Germany). **Suggestion:** See suggestion for line 130 / 3: The timelines resulting from that PICO consolidation process should be added to Figure 3-1	
Roche	10	169/3.1.4 & 372-374/4	According to the process outlined in figure 3-1 and information in section 4, no scoping meeting is foreseen between the assessment team and the HTD, and other stakeholders. Based on the learnings from EUnetHTA JA3 as well as from national processes in various member states, the HTD should have the opportunity to discuss with the assessment team during the scoping phase (e.g. via a scoping workshop/meeting or any alternative way) about PICO survey results, data presentation requirements and potential methodological issues/challenges. PICO(s) provides the basis and sets the framework for the JCA, the HTD must therefore have the opportunity to comment.	
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)	10	Figure 3-1, step 6	Comment: The selection process and composition of the EU patients and clinical experts is neither defined in the EU-HTA regulation nor in this sub-deliverable. However, these stakeholders can potentially have a significant impact on the outcome of the scoping process (cf. comments to page 9, line 138 and page 19, line 354). We recommend to include the missing inclusion criteria and description of the selection process of EU patients and clinical experts in the present document, or if it is part of another sub-deliverable, to refer to it.	
Sebastian Werner vfa	10 19	Figure 3-1, steps for the scoping process 349-357/3.3	The guideline states that EU patients and clinical experts will validate the consolidated PICO(s). According to chapter 3.3 "**PICO validation**", CSCQ members as well as **patients and clinical experts** should comment on the consolidated PICOs. The document should clarifiy the procedural aspects of the "validation" and how the input of the patients and clinical experts is used in that process. It needs to be clarified what	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			documents or information will be used for preparation of the patients and clinical experts. A detailed process for involving EU patients and clinical experts into the scoping process should be given.	
Roche	10	Figure 3-1, steps for the scoping process	EU patients and clinical experts will validate the consolidated PICO(s). The guideline does not give a definition of what "validation" after PICO consolidation means nor does the guideline describe how the patients and clinical experts will be involved and what documents will be used. The process for involving EU patients and clinical experts into the scoping process should be part of this public consultation. A definition for "validation" should be given.	
Roche	10	Figure 3-1, steps for the scoping process	The input from EU patients and clinical experts should be made transparent to the HTD latest with information of the HTD about the final PICO(s). Ideally, such input will be shared with the HTD at suitable interactions during the scoping process (such as a scoping meeting). This step should be incorporated into the description of the scoping process.	
Roche	10	Figure 3-1, steps for the scoping process	Please clarify the first part of the figure by: 1) adding "submission of a letter of intent by the HTD" as an explicit step; 2) adding the JCA secretariat as the creator of the PICO survey; and 3) adding the timing of the letter of intent at the beginning of the scoping process.	
Sallie Latimer, Lumanity	10	Figure 3-1	Please include additional milestones on timeline. Based on previous correspondence, we understand there will be only 55 days between communication of validated final PICOs to HTD and submission dossier by HTD. Please consider if there are any ways in which this timeframe can be extended. Please also reconsider the potential benefit of including the HTD within the scoping process. The HTD often have up to date research on clinical guidelines / guidance and real-world clinical practice that could help inform the relevant PICOs and make the MS consultation process more efficient. The HTD will also need to start preparing the submission dossier prior to validated final PICOs availability. If the HTD was included in the scoping process in the same manner proposed for the MS, up to date research could be shared and any discrepancies between the HTD research and MS consultation highlighted at PICO consolidation; this would allow the HTD more time to prepare for any unexpected PICOs. Within the current process and timeframes proposed, it	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			is unlikely that any unexpected PICOs can be addressed in full in the submission dossier.	
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)	10	Figure 3-1, step 2	Comment: While the responsible party during EUnetHTA is usually mentioned in the respective steps of this diagram, this is not the case for the PICO survey (step 2). We recommend to include the responsible party for the PICO survey in the diagram. Suggestion for rewording: *"Creation of PICO survey by JCA secretariat"*	
Advanced Medical Services GmbH	10	Figure 3-1	"Information available for the survey" and "PICO survey": Add the way how the Member States and their national stakeholders receive the information that is necessary for drawing up Member States' PICO surveys. Specify the documents and their content that are forwarded to Member States and who forwards the documents. Currently only "claimed indication", "posology" and "route of administration" are included in the text box. Will this be sufficient information to develop Member States' PICO surveys?	
Advanced Medical Services GmbH	10	Figure 3-1	Duplicate "Steps for the scoping process": one figure showing the provisional scenario in EUnetHTA 21 (only two JCAs are planned during EUnetHTA 21) and one figure showing the final solution according to the provisions of the HTAR.	
AIM – International Association of Mutual Benefit Societies	10	3.1.4 Expected inputs to the PICO survey	MS ~~should~~ must identify the relevant population(s) for the assessment scope, based on the claimed indication (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	x
Dr. Thomas Ecker, Ecker + Ecker GmbH	10	Section 3.1.4 (Figure 3-1)	**Comment:** In the current draft, no timelines are specified except for submission of the dossier. Specific timelines for all steps depicted in figure 3-1 should be determined. Figure 3-1 only refers to medicinal products, at present, no timelines for medical devices are specified.	
Prof. Matthias P. Schönermark,	10	Figure 3-1, step 9	Comment: In view of the tight time constraints under the EU-HTA regulation and especially during EUnetHTA 21, precise deadlines are needed to create reliability and trust for all	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)			stakeholders. The latest time at which the HTD might learn which PICO requirements must be met is critical to the HTD's project planning. The deadline should be the same in all processes, i.e., already defined, and also as early as possible to enable the submission of a complete dossier for evaluation. We recommend to define the deadline for communication to the HTD and to include it into the diagram. Suggestion for rewording: *"Deadline for communication to HTD" + "D-XXX"*	
Mihai Rotaru - EFPIA	10	169	Figure 3-1 should be completed with clear timelines for each step and should indicate when the process starts. This should also be mapped within both the complete JCA process and against the EMA process	
James Ryan, AZ	10	169	We propose that an additional step is incorporated that provides a HTD proposed PICO or, at least, an assessor's preliminary PICO. This will reduce duplication whilst allowing timely responses.	
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)	11	Intervention	Comment: The PICO to be assessed is specified by the approved indication of a medicinal product. In case a medicinal product is approved as a combination therapy, this is apparent in the label (i.e., indication) and SMPC of the product. The possible scope of application including further mandatory concomitant therapies (i.e., background therapies) are also defined in the SMPC of a medicinal product. Hence, the definition of the intervention to be assessed should be based on the SMPC of a medicinal product and not be up to the opinion of MS or assessor and co-assessor. We recommend to clarify that the definition of intervention including background therapies must be based on the indication and SMPC of a medicinal product.	
Edwards Lifesciences	11	205/ Section 3.1.4 Expected inputs to the PICO survey	Is it ethical to use an off-label comparator when setting PICO? We believe evidence should be obtained from the gold standards. There should be a clear definition on the rules that MS should follow for deciding a comparator, choosing an off-label comparator only as an exception and when justified.	
Edwards Lifesciences	11	209-210/ Section 3.1.4	Is it realistic to use these non-drug interventions ie. Psychotherapy, radiation and physiotherapy?	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
		Expected inputs to the PICO survey		
Norbert Gerbsch for IGES Institut GmbH and HealthEcon AG	11	179 / 3.1.4 Population	**Comment:** To ensure transparency and to avoid misunderstandings that might lead to inconclusive data presentations in the JCA, a comprehensive justification for the definition of any subpopulations requested by the MS should be provided. **Suggestion:** line 179, add: "A comprehensive justification regarding the formation and definition of subpopulations will be provided."	
Norbert Gerbsch for IGES Institut GmbH and HealthEcon AG	11	203+ / 3.1.4 Comparators	**Comment:** The descriptions regarding the comparator do not seem to consider the possibilty that there might not be any relevant comparator at all, e.g. the drug under assessment is the first available therapy for a disease. This could be the case for rare diseases. **Suggestion:** line 210, add: "Depending on the population/disease considered, there might not be any therapy for the disease available at all. This should be noted by the MS accordingly as "best supportive care", "watch and wait", etc."	
Norbert Gerbsch for IGES Institut GmbH and HealthEcon AG	11	203+ / 3.1.4 Comparators	**Comment:** The text suggests that the HTD is expected to always provide comparative evidence even though there might be situations where it is not feasible or ethical to conduct comparative trials, e.g. in some rare diseases. **Suggestion:** line 214, add "The PICO framework should include the possibility that no comparator might be available at all and be considered, i.e. single-arm trials will be considered in the JCA under appropriate circumstances i.e. certain rare diseases."	
Roche	11	173-185/3.1.4	Sub-groups should be reflective of stratification factors defined within the clinical studies and if additional subgroups are selected that they are done so by the basis of clinical practice.	
Roche	11	187/3.1.4	*"The intervention should be defined according to information about the intervention to be assessed".* This is recursive, if you define something based upon itself, it is itself. Suggestion for rewording: "*The intervention is the medicinal product/medical*	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			device for which the HTD seeks EU marketing authorization and whether it is given alone or in combination with other treatments."	
Roche	11	209-210/3.1.4	There is no mention of combination therapies. Consider adding language such as that included within the interventions section: "a comparator could be a monotherapy, combination therapy, with or without best supportive care, and so on."	
Silke Walleser Autiero Medtronic	11	196-202	Contrary to what is stated in line 195, differences in background therapies for medical devices among member states are not rare. This should be considered when allocating time for the consolidation phase.	
Mihai Rotaru - EFPIA	11	204-208	The selection of comparators should follow a structured approach ensuring a final list of comparators that is justified, reasonable and concise. Under ideal circumstances, the priority should be given to established licensed medicines with published robust clinical data, followed by those recommended in European evidence-based clinical guidelines. If this is not possible, routinely used comparators in established clinical practice (if enough robust evidence is available and / or if justified by clinical guidelines) should be considered as long as the evidence submission and assessment of the resulting set of comparators is compatible with the targeted timeline for a high-quality assessment. Furthermore, a process will need to be put in place for situations where no comparators can be defined, e.g. in single-arm trials with high unmet need such as for the development of ATMPs which will be the first one assessed under the HTAR.	
Matias Olsen, EUCOPE	11	195-199	Since the issue with a specific background therapy might be raised more often than currently assumed (MS can have different background therapies, especially with rapidly shifting therapeutics landscape), the guideline should state clear criteria for inclusion of a specific background therapy as part of the intervention. How should different standards of care be dealt with?	
Sallie Latimer, Lumanity	11	Lines 196-200	Discrepancy in proposed approach for handling variations on the intervention relating to background therapy vs dose or timing of administration with the former potentially being included in the final PICO and the latter considered to be potential effect modifiers. Please provide clarity on why these variations would be handled differently. Please also provide clarity on what MS can reasonably expect to be covered at the European	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			vs national level with regard to relevant background therapy. For example, if a single MS reports a difference in background therapy is this considered an applicability consideration at national evaluation? When does it become a European evaluation consideration e.g. when 25% of MS report use, or 50% or >50% etc?	
James Ryan, AZ	11	204-208	The Regulation uses the phrase "best available alternative". Each Member State should therefore provide one comparator for each sub-population. Consequently an AND within a population should not be allowed at a Member State level. If multiple comparators are allowed, then where one Member State uses an OR for comparators within a population, this should be applicable across all Member States. In the final PICO, all these OR options should be provided. Additional complementary analyses can be allowed when a Member State needs an analysis against a specific comparator not included in the European JCA report.	
Tanja Podkonjak – Takeda Pharmaceuticals International AG	11	192-196	The Scoping Guideline current states: "In some cases, a new intervention can be added to, instead of replacing, the standard of care. In these cases, the standard of care 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. 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" Takeda recommends the background therapy or treatment be confined to any background interventions included in the label statement only of the EMA marketing authorisation. The intervention assessed by the HTDs in their pivotal trial used for the regulatory submission may not include the background therapy used in some MS, or it may be applied only to a percentage of the patients in the pivotal trial. The Scoping Guideline does not comment on what would happen in these occasions. We request the guideline be updated to address this situation and that any background therapy considered as the 'Intervention' in the JCA scope be limited to only background treatments or therapies included in the technology's EMA indication statement.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
–Tanja Podkonjak – Takeda Pharmaceuticals AG	11	204-208	The Scoping Guideline currently states: "Comparator(s) could be approved or not (off-label) in the European Union (EU)." The selection of comparators should follow a structured approach ensuring a final list of comparators that is reasonable and concise. Under ideal circumstances, the priority should be given to established licensed medicines with published robust clinical data, followed by those recommended in European clinical guidelines. If this is not possible, routinely used comparators which are recommended by European clinical guidelines and are established clinical practice across multiple MS may be considered if the evidence submission and assessment of the resulting set of comparators is compatible with the targeted timeline for a high-quality assessment. Takeda is concerned that if an off-label comparator is listed in the EU PICO, due to a local treatment pathway deviation applicable for one or very few MS, there may not be available or accessible evidence for the to inform the required analysis and would result in an incomplete JCA dossier. Takeda recommends priority be given to licensed comparators and where ones do not exist, we recommend limiting off-label comparators to only those recommended by EU clinical guidelines or ones which are established clinical practice with sufficient data in the indication in question.	
M. Ermisch – GKV-Spitzenverband	11	196-199	Even in cases where the new HT is added to SOC it needs to be justified why all measures of SOC are to be given adjunct to the new HT. Omission of some measures one would consider to be part of current SOC might be justified, if the HT can prove to be a substitution for these. HTA must allow for this kind of substitution. The full scope of SOC is more important when defining the comparator(s)	
Matias Olsen, EUCOPE	11	187-189	Instead of having this rather unspecific definition for medicinal products, we suggest that the intervention should be defined in accordance with the (draft) SmPC. **Replace:** "The intervention should be defined ~~according to the information about the intervention to be assessed and the indication for which the HTD applied in the regulatory submission dossier~~	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			(in the case of medicinal products) or the … With: "The intervention should be defined **in accordance with the (draft) SmPC** (in the case of medicinal products) or the…"	
GSK	11	179-181	How will consideration be given to the practicality of identifying sub-populations, e.g. to identify if there are sufficient patient numbers available in studies to undertake meaningful analyses?	
Silke Walleser Autiero Medtronic	11	176-178	Usually, the HTD can propose the relevant population (i.e. not only the full population applied for MDR, but also subpopulations)	
Paolo Morgese - ARM	11	204-206	ARM believes that the EU HTA coordination should be consistent with the EU Marketing Authorization process and rules. Requiring comparisons with off-label treatments would generate confusion among stakeholders and would undermine the collaboration between EU HTA and regulatory instances. Joint Clinical Assessment of ATMPs should be consistent with the broader Pharma Legislation and fulfil the highest scientific and regulatory standards.	
Mihai Rotaru - EFPIA	11	195-196	"In rare occasions, this background therapy might differ from one MS to another" The definition of background therapy should also be put in context of the pivotal / registrational study(ies) used for regulatory review and HTA. These background therapies are defined as per study protocol(s), and this (these) study(ies) may not be conducted in all MS (thus, some background therapies may not be available). It would be recommended allowing scientific review and discussions with HTD to limit such risks (feasibility assessment).	
M. Ermisch – GKV-Spitzenverband	11	184-185	As outlined, the starting point for the definition of the relevant population is the population claimed within the SmPC. Thus, MS cannot resolve ambiguities of the claimed indications; they need to be resolved by EMA. However, (sub)populations defined by MS should be formulated unambiguously.	
M. Ermisch – GKV-Spitzenverband	11	205-206	Add: The comparator might also be best supportive care if specific interventions are not available or are not considered to be the sole SoC.	
M. Ermisch – GKV-	11	209-210	See comment in line 196. The MS should define which treatments are considered essential parts of the background	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Spitzenverband			therapy. Proof of added benefit is in principle possible for "new HT + subset of background" vs "background", even if these trials are uncommon	
Matias Olsen, EUCOPE	11	205-206	National policies aimed at cost considerations, such as economic off-label use, should not form the basis for the choice of comparator. It is important that the existing EUnetHTA guidance is taken into consideration. The guidance document "Comparators & Comparisons: criteria for the choice of most appropriate comparator(s)", which is referenced in the project plan indicates a preference for reference treatments according to up to date high-quality clinical practical guidelines at European or national level with good quality evidence on the efficacy and safety profile from published scientific literature, and with an EU marketing authorisation or another form of regulatory approval for the respective indication and line of treatment. Replace: ~~"*Comparator(s) could be approved or not (off-label) in the European Union (EU)."*~~ With: "**Above all, the choice of comparator must be based on available clinical evidence. When the comparator is a pharmaceutical compound, it must have a marketing authorisation for that indication and line of treatment.**	
EFSPI	11	195-196	Current wording: "In rare occasions, this background therapy might differ from one MS to another" The definition of background therapy should also be put in context of the pivotal studies) used for regulatory review and HTA. These background therapies are defined as per study protocols, and these studies may not be conducted in all MS (thus, some background therapies may not be available). It would be recommended allowing scientific review and discussions with HTD to ensure correct understanding of evidence available.	
EFSPI	11	199-200	Current wording: "Variations on the intervention […] do not require a separate PICO". What about interventions that combine medicinal products with an app (e.g. dose guidance)?	
Alexandra	11	201-202	The paragraph describing the intervention for medical devices is not very concise. The HTD	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Poulsson, Norwegian Institute of Public Health			will have described their intervention and therefore it is not clear how configuration and variants will be relevant. It might be better for the MS to focus on the intended uses listed by the HTD and describe which are relevant to them, making sure to clearly describe the clinical indications which are relevant nationally?	
Sallie Latimer, Lumanity	11	Line 174	Terminology that "MS should identify the relevant population(s) for the assessment scope" is misleading when the only relevant population(s) are the full patient population applied for by the HTD and/or subpopulation(s) defined as part of the full population. More accurately the relevant population for the assessment scope should be defined according to the indication for which the HTD applied, and any relevant subpopulation(s) identified by the MS. Please provide clarity on what MS can reasonably expect to be covered at the European vs national level with regard to relevant subpopulation(s). For example, would it be reasonable to include subpopulation(s) that relate to comparator options according to marketing authorization terms at a European level but not subpopulation(s) that relate to comparator options according to local preference or are both considered appropriate for European evaluation?	
Vaccines Europe	11	174	Population: The licensed population, which the HTD is expected to specify at the start of the scoping process, may vary from the recommended target population of an NIP (policy question) (NIP and corresponding vaccination schedule can be a subset of the licensed population). For vaccines targeted at new disease areas no recommendation may exist but vaccines may also target disease areas with existing NIPs, thus, it should be clarified whether for vaccines the licensed population or the target population for an NIP should be specified by the HTD.	
MTE	11	177	**Population.** We call that the MS indicated the indicated population in information on indication reports of interest. Possible complemented by subpopulation of further interest whereby exploratory analysis can be performed.	
Mihai Rotaru - EFPIA	11	178	The HTD should be able to propose in its letter of notification the population that makes sense in order to be aligned with the subsequent national HTA submission. Only those pre-specified in the phase III plan, or requested by the EMA during the assessment should be in scope. EFPIA considers that an EU joint clinical assessment should be based on the EMA population. Sub-populations identified out of interest of national economic (pricing) considerations should not be part of an EU JCA. These considerations were explicitly accounted for in the regulation's stipulation that countries may perform complementary	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			assessments (Recital 15). Although there is a consolidation phase after the PICO survey, it is not specified how for example sub-populations would be considered appropriate or not as the overall approach is not based on a method or principles of evidence-based medicine. Rationale for requesting any sub-population analysis should be also provided. EFPIA proposes that either a methodology based on internationally recognised principles of evidence-based medicine and European evidence-based guidelines are used to establish EU level sub-populations of interest. It is preferable that sub-population definitions should be minimized in order to keep the process manageable. Sub-population can be included in addition to main PICO in the JCA, if justified by medical guidelines/European-based guidelines and if subgroups are aligned with subgroups already pre-defined by the protocol and or statistical analysis plan of the pivotal trials.	
Matias Olsen, EUCOPE	11	178	A maximum number of subpopulations should be defined. Moreover, currently, it is unclear, whether subgroup analyses will be requested in the dossier template. In case subgroup analyses are regularly requested for the submission dossier (e.g. for age, gender), no additional subpopulations should be defined as part of the PICO scheme.	
Matias Olsen, EUCOPE	11	178	Need for further differentiation. Add: "Subpopulation(s): defined as part of the full population. **Subpopulations may also be further differentiated by subgroups (effect modification by specific measures such as age, disease stage, etc.). This should also be specified in the proposed PICO(s).**	
James Ryan, AZ	11	178	Sub-populations. We recommend that the EMA's definition of sub-population is provided as some Member States may use sub-groups and sub-populations interchangeably. (ref: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-subgroups-confirmatory-clinical-trials_en.pdf)	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			For a European assessment, sub-populations should focus on the proposed label and the overall population of the trial(s) on which the indication is based. To align with the Regulation scope, sub-populations based on economic factors should be out of scope and provided at a Member State level through complementary analyses.	
Tanja Podkonjak – Takeda Pharmaceuticals International AG	11	178	Takeda considers that an EU joint clinical assessment should be based on the EMA population (section 4.2.1) and sub-populations of interest out of national funding considerations should not be part of an EU JCA. These considerations were explicitly accounted for in the HTAR's stipulation that countries may perform complimentary assessments. The 'survey and amalgamation' approach to the scoping runs the risk of producing 27 different sub-populations being requested, with many comparators, which may result in a complex JCA process, limiting the HTD ability to conduct the requested analysis thereby limiting its usefulness. Takeda would also like to caution that although clinically relevant sub-populations may be appropriate for EU JCA, conducting these analyses require the use of complex ITC methods leading to greater uncertainty and in many cases sub-optimal analyses (i.e., often breaking of randomization). Takeda is concerned that the proposed survey approach to defining required sub-populations to be analysed in the JCA is not aligned with the objectives of the HTAR, has the potential to request exceedingly complex dossiers which risks delays to patient access. Takeda recommends that either a methodology based on internationally recognised principles of evidence-based medicine are used to establish EU level sub-populations of interest, OR that sub-populations of interest be handled at national level in complementary process.	
BIOTRONIK SE & Co. KG	11	179	Subpopulations to be requested should be kept as predictable as possible, as is the current standard practice in HTA, to enable HTDs to raise best possible evidence. We request the following sentence be added after the first sentence in line 179: Subpopulation requests should be guided by current guidelines, standard of care and known differences affecting treatment outcomes to enable best possible evidence generation. In general MS should provide a reason as to why the separate assessment of a subpopulation is requested.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)	11	179	Comment: The provision of a clear and unambiguous definition of relevant patient population(s) is a prerequisite to enable the submission of a dossier meeting the needs of every MS. This document should clarify that it is imperative for MS to provide a definition of the relevant patient population(s) which meets these quality requirements. We recommend to reword the sentence. Suggestion for rewording: *"[…] must be as clear as possible and avoid ambiguity."* OR *"[…] shall be as clear as possible and avoid ambiguity."*	
Tanja Podkonjak – Takeda Pharmaceuticals International AG	11	185	The Scoping Guideline currently states: "The final definition is used throughout the scoping and assessment phases." Takeda requests the guideline clarify if this refers to the final definition of the population by the assessors. Furthermore, we suggest the addition of rationale column for each component of the final PICO in order to provide clarity for the HTDs and ensure the submission dossier will provide the relevant information and avoid ambiguity or misalignment in the definitions of the population(s) in the PICO(s).	
M. Ermisch – GKV-Spitzenverband	11	188	The word "indication" is used here in the meaning of its definition of the population. Thus, the wording should be changed to better reflect that it is the intended use of the medicinal product that is addressed here (see line 190 ff).	x
BIOTRONIK SE & Co. KG	11	201f	A listing of all available MD configurations and variants (including relevant upcoming updates, frequent software updates, as well as reasonable combinations of individual MDs used together to form a system such as implantable defibrillators) by the assessors preparing the PICO seems unfeasible, as the only entity able to list this with confidence is the HTD. As several MDs are often assessed as a system, an inference as to logical combinations of single MDs from EUDAMED cannot be assumed. The following lines should be added: The HTD will be requested to specify the MDs or combination(s) thereof, outlining possible equivalencies between MD iterations to avoid duplication of assessment efforts.	
MTE	11	203	**Comparators:** Even non EU approved / off label ones? What is the rationale and how can the HD be expected to have data on this? What is the rational for factoring the offlabel used comparators? Is this also applicable for medical technologies or is it only for pharmaceuticals?	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Vaccines Europe	11	204	Population/Comparator: As vaccination (e.g., recommendation and reimbursement status), target populations (e.g., age-based vs risk-based), vaccines (e.g., antigen composition; technology – e.g. conjugated vaccines vs polysaccharide vaccine), vaccination schedules (i.e., age-related timing and number of doses administered) for NIPs targeting the same target population (e.g., infants/young children) vary across EU27, populations and comparators suggested for the national immunisation programme by the EU MS may considerably vary and thus may result in various (sub) PICOs creating a high complexity considering the proposed consolidation approach.	
BIOTRONIK SE & Co. KG	11	205	We suggest that MS be requested to focus on relevant comparators and for this to be specified, to avoid extensive comparison efforts which may not lead to substantial gain in relative efficacy/effectiveness or safety insights. We suggest the addition of the following in line 208: The MS may request an approved or off-label comparator, however, should provide evidence that the suggested comparator is currently being used as the standard of care in the affected country. Therapies expected to receive regulatory approval in the future without current impact on the indication in question may not be requested as a comparator.	
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)	11	205	Comment: According to EU as well as national legislation, pharmaceutical interventions must be approved for each indication in which they are to be used. The permitted application of interventions outside of their approved indication (off-label) is an exception and is subject to detailed regulation. In the present sub-deliverable, cases in which off-label interventions can be considered as comparators and the hierarchy for selection of comparators (e.g., prescribable treatments only, assumption of liability by the manufacturers, approved therapies are to be preferred to off-label therapies, etc.) are not specified. This leads to avoidable uncertainties and potential lack of comparability between HTA procedures. We recommend the addition of conditions under which off-label therapies can be selected as comparator(s).	
GSK	11	205	Guideline suggests that non-approved use of medicines could constitute an appropriate comparator. At minimum, it should be clearly defined under what circumstances this could be the case, e.g. included in clinical guidelines and supported by clinical trial evidence. The guideline should also clarify if this approach intended to be applied for different technologies (including vaccines) or only for therapeutic drugs?	
Dr. Thomas Ecker,	11	209	**Statement in guideline:**	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Ecker + Ecker GmbH			*"A comparator can be not only a pharmacotherapy or a MD, but also other nondrug interventions, such as psychotherapy, radiation, physiotherapy, or surgery."* **Comment:** Specific criteria should be defined for these nondrug interventions. It is currently unclear, how national requirements and treatment standards (e. g. for physiotherapy) are incorporated regarding non-drug interventions.	
Matias Olsen, EUCOPE	11	209	**Relevant text:** Specific criteria should be defined for these nondrug interventions. It is currently unclear, how national requirements are incorporated regarding non-drug interventions.	
Dr. Thomas Ecker, Ecker + Ecker GmbH	11	187–189	**Statement in guideline:** "*The intervention should be defined according to information about the intervention to be assessed and the indication for which the HTD applied in the regulatory submission dossier (in the case of medicinal products)*" **Comment:** Instead of having this rather unspecific definition, we suggest that the intervention should be defined in accordance with the (draft) SmPC. **Suggestion:** "*The intervention should be defined in accordance with the (draft) SmPC (in the case of medicinal products)*"	
Dr. Thomas Ecker, Ecker + Ecker GmbH	11	206–208	**Statement in guideline:** "*If only one comparator out of several options is needed, comparators should be separated by 'OR'. If more than one specific comparator is needed, they should be separated by 'AND'*	

<table>
<tr><th>Comment from</th><th>Page</th><th>Line/ section number</th><th>Comment and suggestion for rewording</th><th>Editorial comment?</th></tr>
<tr><td></td><td></td><td></td><td>

[…].”

Comment:

In the German benefit assessment, besides naming specific medicinal products, in many cases further specifications are stated in order to define the comparator for the assessment in more detail. Common wordings include a “patient-individual therapy”, a “therapy according to physician's choice”, “best supportive care” or a “watch-and-wait approach”. Will such phrases be taken into account when determining the comparators?

If such phrases are taken into account, it is unclear how “small” deviations in the PICOs requested by the MS will be consolidated (for examples, please refer to table 2 and **Error! Reference source not found.** below).

Table 2: Exemplary list of submitted comparators

<table>
<tr><th>Member State 1</th><th>Member State 2</th></tr>
<tr><td>Comparator(s)

~~Could~~ use ~~any of or~~ all required</td><td>Comparator(s)

~~Could~~ use ~~any of or~~ all required</td></tr>
<tr><td>Comparator: therapy according to physician's choice selecting from:</td><td>Comparator: therapy according to physician's choice selecting from:</td></tr>
<tr><td>• medicinal product A</td><td>• medicinal product A</td></tr>
<tr><td>• medicinal product B</td><td>• medicinal product B</td></tr>
<tr><td>• medicinal product C</td><td>-</td></tr>
<tr><td>• medicinal product D</td><td>• medicinal product D</td></tr>
<tr><td>-</td><td>• medicinal product E</td></tr>
</table>

In the scenario depicted in table 2 would all medicinal products (A–E) be included as comparators in the resulting PICO scheme?

</td><td></td></tr>
</table>

<table>
<tr><th>Comment from</th><th>Page</th><th>Line/ section number</th><th>Comment and suggestion for rewording</th><th>Editorial comment?</th></tr>
<tr><td></td><td></td><td></td><td>Table 3: Exemplary list of submitted comparators
<table><tr><th>Member State 1</th><th>Member State 2</th></tr><tr><td>Comparator(s)

~~Could~~ use ~~any of or~~ all required</td><td>Comparator(s)

~~Could~~ use ~~any of or~~ all required</td></tr><tr><td>Comparator: therapy according to physician's choice selecting from:</td><td>Comparator: patient-individual therapy selecting from:</td></tr><tr><td>• medicinal product A</td><td>• medicinal product A</td></tr><tr><td>• medicinal product B</td><td>• medicinal product B</td></tr><tr><td>• medicinal product C</td><td>• medicinal product C</td></tr><tr><td>• medicinal product D</td><td>• medicinal product D</td></tr></table>Would the hypothetical scenario shown in Error! Reference source not found. result in two distinct PICO schemes?</td><td></td></tr>
<tr><td>Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)</td><td>12</td><td>Additional information</td><td>Comment:
Currently, the section “additional information” appears as an unspecific opportunity for the MS to give rather unstructured input and requests that seem contradictory to the otherwise structured and well defined PICO survey. This in combination with discussions “on a case-by-case basis” (line 230) results in uncertainty and may limit the comparability of different procedures.
In addition and as mentioned before (cf. comments to page 9 line 165), a demand of evidence which is not essential for the MS would inflate the scope of assessment and thereby increase the workload for all stakeholders and impede focusing on actually needed and valuable information. Hence, this document should clarify that the obligation of MS to limit their request for evidence to a necessary extend also concerns additional information (e.g., subgroup analyses) requested from the HTD.
Furthermore, it is not clarified whether requests for additional information from the HTD will be consolidated. This would ensure that all MS needs are not only translated into the lowest number of PICO but also least amount of additional information possible.</td><td></td></tr>
</table>

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			We recommend to include a limitation and consolidation of requests for additional information (see suggestion for addition) and provide a clear guideline under which circumstances which kind of information can be additionally requested. Suggestion for addition: *„MS are obliged to limit their requests for additional information from the HTD to the extend necessary for their national decision making. Requests for additional information will be consolidated during the PICO consolidation phase."*	
Edwards Lifesciences	12	216/ Section 3.1.4 Expected inputs to the PICO survey	We look forward to the guidance on endpoints. Knowing that there will be an open consultation on endpoints in October, we will provide comments when that is available. We recommend to ensure that the primary endpoint, which defines the power of the pivotal clinical trial, is also considered as an important criteria in the choice of outcomes.	
Edwards Lifesciences	12	226-227/ Section 3.1.4 Expected inputs to the PICO survey	Background treatments: An early conversation with regulatory/HTA agencies could improve this, to avoid receiving outcomes/comparators that are not included in the evidence generated. We believe that the scoping should involve **early, dynamic and active scientific dialogue** between all relevant stakeholders, including HTA bodies, regulators, health technology developers, patients, clinicians and healthcare professionals involved through the care pathway, being all of them experts on the matter. For the sake of transparency and to have an inclusive approach of the key stakeholders, we believe **the HTDs should be involved across the entire process and participate during the pre-JCA timeframe : PICO definition and the scoping meetings, align on the evidence requirements and on the timelines** required for the submission of the dossier for JCA.	
Edwards Lifesciences	12	240-242/ Section 3.2 PICO consolidation	Consolidation phase: How do you ensure that there is no bias from 1 or 2 member states? If simplification process is not correctly done, it could imply that MS could generate their own HTA appraisal, hence leaving room for potential delays in the access pathway and risk of duplication at the national level, in contradiction to the HTAR core spirit.	
Norbert Gerbsch for IGES Institut	12	215+/ 3.1.4 Outcomes	**Comment:** To ensure PICO compliant data presentation by the HTD, the outcomes requested should be described with sufficient detail, e.g. statistical model, responder analysis using specific threshold etc.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
GmbH and HealthEcon AG			**Suggestion:** line 217, add: "The outcomes requested should be described sufficiently to ensure purposeful data presentation."	
Norbert Gerbsch for IGES Institut GmbH and HealthEcon AG	12	216 / 3.1.4 Outcomes	**Comment:** It seems unclear to what detail outcomes should be listed by MS. **Suggestion:** Add a sample listing to clarify and to avoid strongly differing inputs from MS.	
Norbert Gerbsch for IGES Institut GmbH and HealthEcon AG	12	236 / 3.2	**Comment:** "The objective of the consolidation is to ensure that all MS needs are translated in the lowest number of PICOs possible." The goal to identify the lowest number of PICOs possible is strongly welcomed. Nevertheless the interpretation of Art. 8 (6) sentence 2 of REGULATION (EU) 2021/2282 seems to go beyond the legal provision of the regulation which says: „The assessment scope shall be inclusive and reflect Member States' needs…" „Reflect" leaves room for flexibility while „translate" rather does not. **Suggestion:** Use exact wording of the regulation: Change line 236 to "The objective of the consolidation is to ensure that all MS needs are reflected in the PICO schemes provided." Or alternatively: "The objective of the consolidation is to ensure that all MS needs are fully considered in the PICO schemes provided."	
Norbert Gerbsch for IGES Institut GmbH and HealthEcon AG	12	240+ / 3.2	**Comment**: To ensure transparency, the originally requested PICO(s) that were dropped or integrated during the consolidation process should be documented including respective justifications. No comparator shall be omitted, because otherwise the additional benefit vs. the omitted comparator can no longer be proven. 'Omitted' comparators should at least optionally be included and highlighted. If HTD submits evidence for the omitted comparator, this should also be assessed. Related to the example: If there is evidence for subpopulation A vs. comparator 2 or 3, this would not be taken into account at present. **Suggestion:** line 242, add additional sentence: "The PICOs provided by all MS and the consolidation process will be documented and provided to the HTD together with the final consolidated PICO(s)."	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Roche	12	205/3.1.4	The definition of commonly used comparators should follow a structured approach ensuring a final list of comparators that is reasonable and concise. The priority should be given to established licensed medicines with published robust clinical data, followed by those recommended in European clinical guidelines.	
Roche	12	216-217/3.1.4	"Outcomes" is a very broad concept with many interchangeable terms, but also different terms being used interchangable. For the PICO survey it would be preferred to have an assessment-dependent harmonized list around outcomes terminology for which the manufacturers have been able to provide input to and ensure that the primary endpoint(s) are reflected in this list. This would simplify the process and avoid unnecessary confusion, any additional outcomes requested by MS beyond this list should require a clear rationale.	
Roche	12	236-238/3.2	The proposed process defines separate PICOs for different comparators. In general, we strongly recommend combining PICOs for the same population (regardless of the number of comparators) into one pan-EU PICO. With separate PICOs, there may be ambiguity on which indirect evidence should be used for comparators that have not been studied head-to-head against the novel intervention. This ambiguity can be resolved with a pan-EU PICO (per population), which will guarantee a consistent set of estimates at the EU level.	
Mihai Rotaru - EFPIA	12	233-242	When assessor/co-assessor undertake the consolidation of the final draft PICO (based on results of MS survey) the following guidelines should be foreseen: - Consistency in assumptions of clinical interchangeability of comparators across MS (e.g., if for a same patient population, Comp 1 and 2 are interchangeable in MS 1, and Comp 1 and 3 are interchangeable in MS2, interchangeability of Comp 1, 2 and 3 should be assumed. Deviations of this principle should be justified in the underlying documentation of the final PICO (e.g., Comp 2 not acceptable for MS 2) - No overlaps of research questions: if one patient population represents a subset of another patient population, this should be reflected as a "Sub-PICO" of the latter, rather than a separate research question. This should ensure that effects in subsets vs full population are analysed, evaluated and interpreted in conjunction.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			- Consistency of comparators within patient populations (e.g., if Comp 1 is a valid comparator for the full indication, Comp 1 should be a valid comparator for all subsets of the full indication). Deviations of this principle should be justified in the underlying documentation of the final PICO (e.g. none of the MS requested this comparison).	
Sallie Latimer, Lumanity	12	Lines 222-229	It is not clear what should be considered additional information vs PICO information as all examples given within the "Additional information" section are relating to specific population, intervention or comparator information. Please also provide clarity on what MS can reasonably expect to be covered at the European vs national level with regard to potential effect modifiers within the population and will guidance be made available on the preferred analytic approach to exploring potential effect modifiers?	
M. Ermisch – GKV-Spitzenverband	12	223-229	This paragraph lacks clarity. We understand it in a way that MS can use this section to convey their understanding that within a trial the underlying conditions are treated adequately, especially if the HT addresses an aspect of morbidity that could not be addressed with existing therapy. If so, this should be clarified. Generally, background therapies should be part of the PICO.	
Matias Olsen, EUCOPE	12	223-229	If a background therapy is not named as part of the comparator but is instead listed under "additional information", is the PICO scheme still considered fulfilled if the comparator was correctly implemented in the study but the background treatment therapy listed under "additional information" was not incorporated into the study design? In brief, what are the requirements for the evidence needed in case a background treatment is defined under "additional information"?	
EFSPI	12	223-229	The terms 'outcomes' and 'endpoints' used interchangeably here? Please clarify and/or align across the document	
Matias Olsen, EUCOPE	12	215-219	Are the results of the PICO consolidation, which are shared with the HTD, published transparently including the results of the individual Member States? The requirements stated from the individual Member States are crucial for the national HTA process as well as for pricing and reimbursement.	
Matias Olsen, EUCOPE	12	215-219	It is not clear how detailed the required outcomes of the PICO schemes that will be defined by the Member States are. Will all required endpoints be directly mentioned, including the most suitable operationalisation (e.g. "PRO XY with MCID of Z") or will it be more general	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			leaving a degree of freedom for interpretation ("present all patient relevant endpoints for the categories mortality, efficacy, quality of life, safety")? As different Member States might have different views on the operationalisation/statistical analysis criteria for endpoints, further information that go beyond what is described in deliverable D4.3.2 "Methodological guideline on Direct and Indirect comparisons" will be critical.	
Matias Olsen, EUCOPE	12	215-219	The detail of the listed outcomes should be specified. To ensure PICO compliant data presentation by the HTD, the outcomes requested should be described with sufficient detail, e.g. statistical model, responder analysis using specific threshold, for example 0.7 HR, etc. Add: "MS are expected to define their needs by listing several outcomes. **The outcomes requested should be described in a sufficient manner to ensure purposeful data presentation.**".	
Sallie Latimer, Lumanity	12 17	Lines 216-219 Lines 332-334	In the absence of any value judgement or ranking to outcomes / endpoints, the all-inclusive approach proposed could result in a non-exhaustive list of outcomes / endpoints, several of which may not be relevant to the HTA. Please consider providing MS with more detailed guidance on outcomes / endpoints that should be included, and clarity on if the choice of endpoints 'might' or 'should' be informed by guidance developed in Joint Action 2. There is discrepancy on this on page 12 where it is stated the choice of endpoints 'might' be informed by guidance versus page 17 where is is stated guidelines on the selection of outcomes 'should' be followed. Please more generally reconsider the potential benefit of asking MS to highlight critical vs important outcomes / endpoints as part of the survey so this information is available to HTAR assessors, even if this detail is not included in the final PICOs. This would avoid the need for further consultation where evidence are not available for all outcomes / endpoints proposed.	
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake,	12	240-242	Comment: Since the selection of PICOs has a major potential impact on the outcome of the HTA process, PICO consolidation must be comparable between different procedures, individually comprehensible, transparent and, above all, binding for the MS (assuming a consistent label). This applies to every step of the scoping process. Thus, if a MS deviates from its	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Ph.D. (SKC)			initially required PICO in the course of a discussion of options for consolidation, this must be documented. We recommend to define and explain the formal processes of open questions and discussions of options for consolidation in more detail.	
M. Ermisch – GKV-Spitzenverband	12	240-242	This sentence requires comments on two aspects: 1st: It is adequate to allow for checking back to clarify ambiguities. 2nd: These check backs should not be limited to the aim of reducing the number of PICOs, but also to clarify any ambiguities. However, this might result in a need for member states to repeat decision finding, which might pose a problem for timelines	
Liebenhoff, BAH	12	240 - 242	"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." It is crucial to minimize the account of PICOs, as it is written in lines 236 – 237: "The objective of the consolidation is to ensure that all MS needs are translated in the lowest number of PICOs possible." For that, compromises need to be made. Therefore, we propose the following amendment: "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 and compromises for consolidation."	
Matias Olsen, EUCOPE	12	240-242	The HTD should be involved in the definition of the PICO(s) to ensure a robust dossier submission, and their feedback can play an important role in its consolidation. Add: "To achieve the fewest PICO(s) possible during the consolidation phase, the assessors/co-assessors might contact the MS **as well as the HTD** to clarify open questions resulting from the PICO survey and discuss options for consolidation. **During the consolidation process sufficient time will be granted for the HTD to comment on the PICO schemes and to request clarification on inexplicit aspects.**	
Matias Olsen,	12	240-242	To ensure transparency, the originally requested PICO(s), also including those that were	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
EUCOPE			dropped during the consolidation process should be published or at the least shared with the HTD, with respective justifications. Add: "…consolidation. **All the individual PICO(s) provided by MS and the consolidation process will be documented and communicated to the HTD together with the final consolidated PICO(s).**".	
Mihai Rotaru - EFPIA	12	240-241	PICOs provided by different MS could differ very slightly and may not be consolidated efficiently. However, the differences between the PICOs might not be key to individual MS decision making. The document states "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.". The assessor/co-assessor should not only be given an opportunity, but actively encouraged to consolidate the differences in order to minimize the workload of the assessment and to reduce chance findings from multiple analyses.	
James Ryan, AZ	12	237-238	A PICO traditionally focuses on one population and may have multiple comparators. This should be used rather than separate PICOs for each comparator within the same population.	
Alexandra Poulsson, Norwegian Institute of Public Health	12	237-238	"One PICO comprises one population, one intervention (or combination), one comparator (which can include more than one medicinal product), and...." should include medical device: One PICO comprises one population, one intervention (or combination), one comparator (which can include more than one medicinal product or one or more medical devices), and.....	
EFSPI	12	205	Current wording: "Comparator(s) could be approved or not (off-label) in the European Union (EU)." This definition is too broad. Proposed rewording: "Comparator(s) could be approved or not (off-label) but commonly used in the European Union (EU), as supported by an assessment of use in the market"	
M. Ermisch – GKV-Spitzenverband	12	214	Add: If as the intervention, a MD is used in addition to SOC and its use relies on a surgery or interventional procedure, the effects of any sham intervention in addition to SOC must be taken into account.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Mihai Rotaru - EFPIA	12	215	The choice of endpoints for a joint clinical assessment should be based on expert knowledge of the clinical literature to ensure that complex evidence networks can be assessed using the same endpoints. In complex networks, trials may have been performed in very different time periods where the use of endpoints may have evolved. Feasibility is an important consideration in selecting the appropriate endpoints to facilitate multiple comparisons of the new technology. EFPIA believes that, as a principle, an EU joint clinical assessment should rely at a minimum on all EMA accepted endpoints, plus PROs, plus, at an ITT level only, safety. If MS would like to include additional outcomes in the assessment scope, the justification should be made in line with principles of evidence-based medicine, and this information gathered during the PICO survey by the countries should be made visible to the HTD to allow to them to prepare for potential complementary (unavoidable) request and submissions (predictability both for HTD and MS).	
James Ryan, AZ	12	215	EMA assessed endpoints should be included as a minimum in the European assessment, in addition to commonly requested endpoints from Member STATES. These EMA endpoints could be added in a proposed PICO by either the HTD and/or assessor at the start of the survey.	
BIOTRONIK SE & Co. KG	12	216ff	Given that document JA2 was developed in a previous iteration of EUnetHTA with a different mandate, we suggest this document to be adjusted to the new mandate.	
Mihai Rotaru - EFPIA	12	217	We suggest indicating that the corresponding EUnetHTA21 public consultation will occur in October and to list the range of outcomes currently considered (safety, clinical endpoints, surrogate endpoints, quality of life).	
Tanja Podkonjak - Takeda	12	221, 230-231	Current text: 'MS could use this section to provide additional information for the assessor/co-assessor.' Please provide further clarity on the types of additional informaton the MS may request. For transparency and efficiency, we request that additional information be limited and suggest a catalogue of potential additional information be pre-speficied and shared with HTDs and MS. Furthermore, we request the HTD be included in a scoping meeting so that the feasability of the additional request can we discussed.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Mihai Rotaru - EFPIA	12	222	Related to the number of PICOs, multiplicity issues and potential Type I and II errors will arise. Further consultations between JCA, MS and HTD should be planned in the process to assess implications and possible mitigations.	
Mihai Rotaru - EFPIA	12	222	The guideline should clarify if MS will provide potential effect modifiers by indication or therapeutic area to be more comparable across dossiers and if sponsors are expected to select/subsect of those potential effect modifiers?	
BIOTRONIK SE & Co. KG	12	222	Effect modifiers, specifically in MDs, are plentiful and often impossible to assess, e.g. implanting clinician's experience and qualification. Therefore, we request the following to be added to line 222: Any additional requests should be strictly specified in terms of scope and contain justification from the MS on why this may be required, feasibility of assessment and how exploration of the modifier will improve final assessment outcomes.	
Matias Olsen, EUCOPE	12	222	Currently, it is unclear, whether subgroup analyses will be requested as part of the dossier template, or if it will be restricted to primary outcomes. In case subgroup analyses are regularly required as part of the submission dossier (e. g. for age, gender), no additional requests for analyses of potential effect modifiers, which have been raised by single member states, should be considered. Due to the short timeframe between definition of PICO schemes and dossier submission, a predictable framework for required analyses is essential to deliver analyses within this short time period.	
GSK	12	222	Will MS provide potential effect modifiers by indication or therapeutic area to be more comparable across dossiers? Will sponsors select subsect of those potential effect modifiers?	
James Ryan, AZ	12	222	It may be beneficial to refer to sub-groups here, which is aligned with how Member States may think about PICOs. We recommend using the EMA definition on sub-groups (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-subgroups-confirmatory-clinical-trials_en.pdf, see 1st paragraph 4.1) and replace this line so that only credible and biologically plausible sub-groups that could be treatment effect modifiers and have been pre-specified or considered of importance by the EMA are included.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			Additional sub-groups, particularly those non-prespecified as being potential treatment effect modifiers, should be out of the PICO scope for a clinical assessment that is establishing the relative or incremental benefit of a new treatment versus another. Consideration of laws relating to inequality and discrimination and their applicability to final decision-making at a Member State level should be given when requesting sub-groups. Where recommendations cannot be based on such sub-groups they should be excluded from the European PICO.	
EFSPI	12	222	In order to increase predictability and comparability across dossiers, it is suggested that potential effect modifiers are also considered on a therapeutic area basis (not just by indication)	
Tanja Podkonjak - Takeda	Page 12	222	The Scoping Guideline states, "MS could request to explore potential effect modifiers within the population (e.g., age, sex, dose, etc.)." We understand this exploratory information may be of interest for MS for economic decision making, however we are concerned about the practicality and data integrity of conducting such analyses. Takeda respectfully requests that, as commented previously, a rationale for the request to explore potential effect modifiers is provided by MS and carefully considered by the assessor and co-assessor in the consolidation of the PICO(s). Furthermore, we respectfully suggest that the Scoping Guideline removes the word potential from this line and states that "MSs could request to explore effect modifiers (e.g., age, sex, dose, etc.) however these requests must be supported by a strong clinical rationale. This way the data associated with effect modifiers that HTDs include adds value to the evidence provided in the submission dossier. The current approach risks having a considerable amount of information and data on the impact of effect modifiers that are not supported by clinical rationale for the intervention and indication and may cause additional noise (in an already constricted timeline) but not ultimately be informative for the JCA.	
MTE	12	222	**Explore potential effect modifiers, specify specific national care approaches.** This will be a critical part of information especially for the complex interventions the targeted medical technologies are. We therefore call for an involvement of the HTD in the scoping process to indialogue with he HTACG defines the confounding factors and covariates to be accounted for.	
Mihai Rotaru -	12	232	The final consolidation and definition of the PICO relevant for the joint clinical assessment	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
EFPIA			should be based on clinical criteria only. A method for selecting and filtering the populations, comparators and outcomes is required based on the principles of evidence-based medicine.	
Matias Olsen, EUCOPE	12	236	Replace: "The objective of consolidation is to ensure that all MS needs are ~~translated in the lowest number of PICOs possible.~~". With: "The objective of consolidation is to ensure that all MS needs are **fully considered in the PICO schemes provided.**".	
MTE	12	241	**Discuss options for consolidation.** A process of validation by the HTACG seems to be missing. This also enabling to define what will be covered by JCA and what further will need to be addressed at national level.	
Dr. Thomas Ecker, Ecker + Ecker GmbH	12	215–219	**Comment:** With regard to the national HTA, it would be helpful to know which member states requested which endpoints.	
EFSPI	13	289-301	Should we apply a, b and c in order? For example, firstly check one comparator, then 'AND scenario, lastly 'OR' scenario.	
GSK	13	254	Format of cell 'Comparator' is not user friendly. For example, suggest adding 'or/and' cell (or dropdown button) between comparator 1 and comparator 2 instead of crossing out 'all required' in first row.	
EFSPI	13	254	Format of cell 'Comparator' is not user friendly. For example, suggest adding 'or/and' cell (or dropdown button) between comparator 1 and comparator 2 instead of crossing out 'all required' in first row.	
MTE	15	289	Even if only one MS requires a comparator, it is added to the list – this will lead to an incredible burden for the HTD and is not realistic.	
Sebastian Werner vfa	16	296-297/3.2.3	The guideline describes an algorithm for the definition of the assessment scope based on a PICO survey and a subsequent **consolidation process**, which aims at minimizing PICO. According to this, for every population, all comparators are selected, however, the lowest number of comparators needed to satisfy the requirements for all MS will determine which comparators will be selected.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			This minimization process is per se problematic, as it **potentially eliminates relevant comparators** leading to exclusion of high-quality evidence (RCTs) from the European assessment. Example: -MS1: treatment 1 -MS2: treatment 2 -MS3: treatment 1 or 2 or 3 In this scenario comparators 1 and 2 would be chosen and comparator 3 excluded. However, this comparator might be included in the approval study. This would lead to an **exclusion of high-quality evidence** (RCTs) from the European assessment. The concept for the scoping process and the consolidation process must be fundamentally revised. The concept must put more emphasis on the evidence generated by the HTD and include principles that can drive harmonization. The scoping process must streamline the MS questions and aim for a harmonized EU PICO that is guided by the generated evidence.	
Norbert Gerbsch for IGES Institut GmbH and HealthEcon AG	16	293-301 / 3.2.3	**Comment:** Character c): Please clarify sentence 5. **Suggestion:** Line 299, add before "Again, a separate PICO..": "The remaining comparators are listed stating the MS and marked as optional. If HTD submits evidence for these optional comparators, this is also assessed."	
Roche	16	293ff/3.2.3	"Select 'OR' comparators" Example: -MS1: proposes drug 1 -MS2: proposes drug 2 -MS3: proposes drug 1 or 2 or 3 If EUnetHTA selects only the overlapping comparators (drug 1 and drug 2) to reduce the number of PICOs it could happen that drug 3 which might be the comparator in the approval study is not selected. Direct evidence would be missing and a comparator which is seen as equal to the other drugs would not be taken into account. This situation should be avoided. The comparator used in the pivotal	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			study should appear as comparator in the PICOs in any case.	
Matias Olsen, EUCOPE	16	297-299	Replace: "…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.". With: "…If no preference can be given, this will be highlighted. **In any case all mentioned "OR" comparators will be included in the PICO scheme for the respective MS as alternative options.** This means that the HTD can choose the most relevant comparator from the options presented.".	
M. Ermisch – GKV-Spitzenverband	16	308-309	see above comment on line 296 - 297	
M. Ermisch – GKV-Spitzenverband	16	313-314	This conclusion is only correct, if while using comparators 3 and 4 in a study, statistical power is sufficient to give valid results for a subgroup analysis for comparator 3 or if MS 2 is willing to accept results from the complete study population to be valid for his comparator, because effect modifications were absent.	
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)	16	3.2.3	Comment: In case of "OR" comparators the current draft stipulates that the lowest number of comparators needed to satisfy the requirements for all MS will determine which comparators will be selected. The comparator definition would therefore only include alternate options if "no preference can be given". However, there are several reasons why the best possible evidence for an HTA might not be available for all "OR" comparators: •The number of JSCs available will not be sufficient to conduct a JSC for every medicinal product that has to undergo a JCA. Hence, many HTDs will have to design their clinical trials based on assumptions which PICOs will be required. •Even if a JSC took place, changes in the standard of care may occur between the JSC and application for marketing authorisation, which may affect the required comparators. •In the case of orphan drugs, conduction of RCTs might not be possible due to too few	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			affected patients or might not be ethical. Under the current draft it could therefore happen that a possible comparator for which the best evidence is available is not included and the HTA has then to rely on evidence, which might not be accepted as methodologically sufficient (e.g., historical comparisons, insufficient similarity and homogeneity of RCTs for indirect comparisons). On national level this could result in a benefit resolution granting no added benefit – due to methodological issues but not due to an actual lack of an added benefit – although an added benefit of the medicinal product could have been proven if the other "OR" comparator had not been excluded. To enable the submission of a dossier containing the best available evidence, the HTD needs to be informed about all potential "OR" comparators for all MS. Preferred comparators i.e., comparators that are required by further MS could be highlighted. We strongly recommend to revisit the consolidation approach for "OR" comparators.	
Mihai Rotaru - EFPIA	16	293	EFPIA suggests the elimination of "OR" comparator options that are not required by all MS for a specific population. Comment: The Scoping Guideline requires the elimination of "OR" comparator options that are not required by all MS for a specific population. It says that: "The lowest number of comparators needed to satisfy the requirements for all MS will determine which comparators will be selected." In the example given, Comparator 2 will be eliminated from the PICO for Subpopulation B because Comparator 3 is acceptable to both Member State 2 and Member State 3 for Subpopulation B but Comparator 2 is only acceptable as an alternative to Comparator 3 for Member State 3. Consider the following scenario based on the example given in the Scoping Guideline: The HTD has conducted an interventional study comparing the Intervention to Comparator 2 in Subpopulation B. The HTD would be able to demonstrate superior efficacy and equal safety of the Intervention to Comparator 2 from the study. However, the HTD had not done so for Comparator 3 Due to methodological problems demonstrating superior efficacy and equal safety in an indirect comparison might prove much more difficult for the HTD. The removal of Comparator 2 from the PICO for Subpopulation B would preclude the HTD from providing relevant high-quality information to Member State 3 regarding Comparator 2 for its policy decisions and would do so at no additional gain for Member State 2. This information about Comparator 2 might be relevant to many MS (MS 4, 5, 6, and 7 for example), but because it is not relevant to Member State 2, no other MS would be able to benefit from it.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			Suggestion for rewording: "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 all MS will determine which comparators will be selected. They will be part of the core PICOs. To provide the opportunity for HTD to also use clinical evidence vs a comparator being nominated by a MS, but not finally selected in the consolidation process, optional PICOs should also be considered for JCA. As a consequence, the HTD will be asked to provide data on the core PICOs but may choose to provide additional data for optional PICOs for JCA as well. If the HTD chooses to do so, the additional evidence will be treated equally to all other data provided during the HTA process. 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." Subsequent sections will need to be reworded as well to be aligned to this section.	
EFSPI	16	293	Current wording: "Select 'OR' comparators" Example: - Member state 1: drug 1 - Member state 2: drug 2 - Member state 3: drug 1 or 2 or 3 If assessors selects only the overlapping comparators (drug 1 and drug 2) to reduce the number of PICOs it could happen that drug 3 which might be the comparator in the pivotal study used for EMA approval is not selected. Direct evidence would be missing and a comparator which is seen as equal to the other drugs is not taken into account. This situation should be avoided. The comparator used in the pivotal study should appear as comparator in the PICOs	
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake,	16	328	In the current draft the consolidation approach for "OR" comparators would only lead to inclusion of alternate options in the comparator definition if "no preference can be given". Subsequently, for the example of subpopulation A neither Comparator 2 nor Comparator 3 would be chosen. However, line 328 currently contains a double negative, which would imply that both comparators are chosen instead of none.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Ph.D. (SKC)			In case the consolidation approach for "OR" comparators is not revisited to always include all possible "OR" comparators (see comment to page 16, section number 3.2.3), we recommend to delete the double negative. Suggestion for rewording: *"[…] neither comparator is ~~not~~ chosen."*	
M. Ermisch – GKV-Spitzenverband	16	296.297	If the lowest number of comparators to satisfy the requirements for all MS will determine, which comparators will be selected, this results in information loss. Provided, 3 MS would accept comparators A OR B and one MS would accept comparator A only, it is true that by choosing comparator A, the HTD could fulfil all MS needs. However, he might prefer using comparator B, even when this means losing one MS; e.g. because a RCT comparing the HT to B is available. By consolidating in the prescribed way, the information is lost, that comparator B would be sufficient for 3 out of 4 MS. Thus, this cannot be supported if it results in the loss of appropriate direct comparisons.	
Norbert Gerbsch for IGES Institut GmbH and HealthEcon AG	17	333 / 3.2.4	**Comment:** "In principle, all outcomes should be included for all PICOs." The resulting PICOs are directly related to the MS, whose requirements lead to a respective PICO. Therefore it seems incomprehensible to include „all outcomes" even outcomes of MS which are not related to a respective PICO but taken into account in another PICO. **Suggestion:** Clarify line 333 as follows: „For each PICO, all requested outcomes for the respective MS are to be considered, but not all outcomes from all MS."	
James Ryan, AZ	17	332-334	"In principle, all outcomes should be included for all PICOs" This will potentially lead to redundant analyses and excessive workload for all stakeholders. Please see earlier example under general comments. As part of the consolidation, the assessors should take account of how common the request is for the outcome (i.e. do only a minority of Member States need it) in each population and the underlying evidence base. Where only a minority need it, that outcome should not be included and should be addressed as a complementary analysis. The assessors should also consider the underlying evidence base available to further consolidate a streamlined PICO(s).	
Matias Olsen,	17	333-334	There needs to be a selection of a maximum set of outcomes to be considered in the	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
EUCOPE			assessment, in order to not overburden the procedure, while in principle addressing each requested outcomes, according to the guidelines for selection of outcomes. Replace: "…the selection of outcomes should be followed.[9,10,11,12,13] ~~In principle, all outcomes should be included for all PICOs.~~" With: "…the selection of outcomes should be followed.[9,10,11,12,13] **For each PICO, all requested outcomes for the respective MS are to be considered, and not all outcomes from all MS.**".	
Sebastian Werner vfa	19	364-368/3.4	The guideline states that in case the CHMP opinion recommends a different indication from the one initially applied for, an update of the PICOs is expected and the evaluation process will be delayed. The guideline asks for a solution that is needed to account for the **risk of labelling change**. The authors mention the possibility of the cooperation between the assessor/co-assessor and the corresponding regulatory team, according to HTAR Article 15(1) as a possible solution, however they do not discuss how this cooperation can mitigate the risk of labelling change. Changes in label can have a strong impact on the clinical assessment in Germany as data requirements can substantially change. According to a vfa survey, in approx. 8%-12% of the procedures in Germany a relevant change in the label occurs that lead to a substantial change in data requirments. A separate procedure must be put in place to deal with cases of labelling changes. The detailed timelines and changes to the standard procedure needs to be clarified. It should be also clarified how the cooperation between assessor/co-assessor and regulatory team can mitigate the risk of labelling change.	
Norbert Gerbsch for IGES Institut GmbH and HealthEcon AG	19	354 / 3.3	**Comment:** Based on REGULATION (EU) 2021/2282 Art. 8 (6) sentence 4 CSCQ members as well as patients and clinical experts are invited to comment on the consolidated PICOs. However the regulation wording is as follows: „The scoping process shall also take into account information provided by the health technology developer and input received from patients, clinical experts <u>and other relevant experts</u>." It is therefore explicitly open for other relevant experts. The HTD undoubtedly is an expert of the health technology in question.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			Therefore HTDs should be given the chance to comment on the consolidated but not yet adopted PICOs as well. **Suggestion:** "CSCQ members as well as patients, clinical experts and HTD as relevant experts are invited to comment on the consolidated PICOs."	
Norbert Gerbsch for IGES Institut GmbH and HealthEcon AG	19	365 / 3.4	**Comment:** It is clearly stated that a solution for this risk is needed but no solution/timeline offered. It is fully acknowledged that it is extremely difficult to suggest a solution given the strict timelines imposed by REGULATION (EU) 2021/2282. Nevertheless it seems necessary to present suggestions as otherwise this might develop into a problem that threatens the successful application of the regulation in its entirety. **Suggestion:** Add a a suggestion in line 365 such as „The implementation of stop clock procedures as regularly used in EMA-processes might offer a solution to deal with inevitable delays caused by label changes and should therefore be considered.“	
Roche	19	350-357/3.3	The results of the survey (i.e. summary of individual PICOs submitted by each HTA body), consolidation tables, and the proposal for consolidated PICOs must be shared at the same time as the CSCQ JCA meeting and discussed with the HTD. PICO(s) provides the basis and sets the framework for the JCA, the HTD must therefore have the opportunity to comment.	
Matias Olsen, EUCOPE	19	349-357	The HTD must be given the opportunity to discuss the PICO with the authorities, experts and patients. The meeting should not exclude the HTD. So far, no participation of HTD in the process of PICO consolidation is foreseen, which as mentioned above, is a deviation from existing EUnetHTA JA3 guidance and established procedures. HTD that are subject to a joint EU HTA should have the opportunity to address open questions regarding the scope of the assessment and the evidence to be included within the PICO consolidation process and to explain their rationale. The current lack of exchange between HTD and EU HTA bodies is a major point of concern. All HTD should be offered the opportunity of exchange with the EU HTA bodies within the process of PICO consolidation.	
–Tanja	Page 19	Table 3-8	The example provided in the Scoping Guideline, the text states:	X

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Podkonjak – Takeda Pharmaceuticals International AG	Page 21	392-393	"Note that only the first chapter has three subsections because it encloses three different comparators (Comparator 3, Comparator 4, and Comparator 1 OR 2)." It is not clear who would decide between Comparator 1 OR Comparator 2 in the example provided. In an 'OR' situation, if the Guideline foresees the HTDs having the liberty to provide evidence for (i.e., the HTD's decision), Takeda request that the Scoping Guideline makes this explicit so HTDs can proceed under such guidance. If this decision is not up to the HTDs, the Scoping Guideline should explicitly state who is the decision maker and that the selected comparators will be explicitly communicated to the HTDs when 'OR' is used for comparators in a given PICO.	
Silke Walleser Autiero Medtronic	19	366 - 370	We agree with the importance of establishing rules for the cooperation between Assessors/Co-assessors and regulatory bodies. It is likely that the key cooperation with groups involved in the regulatory process are the expert panels because, by the time a medical device dossier goes to the expert panel, it has already been reviewed by the Notified Body. It will be very important to clearly distinguish and define the roles of the expert panels in collaboration with HTA assessors, vs their roles within MDR, considering that the two processes are distinct and serve different purposes.	
M. Ermisch – GKV-Spitzenverband	19	366-368	The problem description is valid. However, even closer cooperation between HTA and EMA cannot solve this problem. It might help partially, if EMA could flag products, where changes between the currently proposed indication and the final indication are likely to happen. Anticipating the final result cannot be possible, otherwise the last discussions between EMA and HTD in preparation of the CHMP opinion would not be necessary.	
Matias Olsen, EUCOPE	19	363-365	We do agree, that a detailed concept for handling of labelling changes has to be developed. At this moment, no timelines for this scenario have been defined, however, a concrete timeframe is essential to ensure high quality of the submitted data. Firstly, it is currently unclear what the timeframe is for updating the PICO schemes. Moreover, in this context, we would like to point out, that labelling changes and the resulting adaptions/changes in PICOs might require modified or even completely new data analyses. However, data analysis can be very time consuming (up to several months depending on the scope of these analyses). Moreover, the newly generated data then needs to be incorporated into the dossier, which also requires time. Will there be a defined mechanism of interaction between HTD, EMA and EU-HTA bodies to	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			enable an early exchange between the involved stakeholders in case of labelling changes? Labelling changes might already be discussed at earlier timepoints in the regulatory process – in these scenarios, it will be essential, that these upcoming changes are communicated as soon as possible, especially if these changes result in modifications of the PICO schemes. Only in this way, will it be possible to adjust the dossier in a timely manner. Because a labelling change cannot be covered by the clinical studies and the EMA also uses the study data for authorisation, the posology used in the clinical trials should also be used for the JCA. Change of the PICO should be discussed in a joint meeting with the HTD.	
Matias Olsen, EUCOPE	19	366-368	We welcome the fact that a close cooperation between the regulatory team and assessors/co-assessors is envisaged. However, we are convinced that HTD should be involved in this exchange providing insight into the new medicinal product and its development in order to allow for a fruitful cooperation between the stakeholders involved in the EU-HTA procedure.	
M. Ermisch – GKV-Spitzenverband	19	355-356	The proposal seems to indicate that within the validation, changes to the PICOs would be possible. Provided, no errors occurred during the compilation, there seems to be no option for changes. Thus, it is unclear, why more than a vote in writing upon correctness of the results is necessary and how additional input shall be considered.	
Matias Olsen, EUCOPE	19	354-355	Add: "CSCQ members as well as patients, clinical experts **and the HTD** are invited to comment on the consolidated PICO.".	
EFSPI	19	240-241	Current wording: "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.". PICOs provided by different MS could differ very slightly and may not be consolidated efficiently. However, the differences between the PICOs might not be key to individual MS decision making. The assessor/co-assessor should be not only given an opportunity, but should be encouraged to consolidate the differences in order to reduce chance findings from multiple analyses, and endanger timely medicines provision.	
EFSPI	19	366-367	Current wording: "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	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			explored whether this could contribute to a solution." A further evaluation of the benefits and risks of collaboration between regulatory body/bodies and HTA JCA assessor/co-assessor and JCS reviewers should be encouraged to incorporate HTA and PICOs aspects at the clinical development design stage.	
Paolo Morgese - ARM	19	355-356	ARM is concerned of PICO selection based on consensus and not on qualified majority as it puts the scoping process at risk of being incloncusive.	
Dr. Thomas Ecker, Ecker + Ecker GmbH	19	Section 3.3	**Comment:** So far, no participation of HTD in the process of determining the assessment scope is foreseen. The experience of Joint Action 3 highlighted that it is important to have meetings among accessors and HTD to promote a shared understanding of the appropriate assessment scope. In this context, input from HTD is crucial to ensure the best possible submission. Thus, the HTD should have the opportunity to discuss with the assessors/co-assessors the PICO schemes and to address open questions regarding the scope of the assessment and the evidence to be included within the PICO consolidation process and to explain their rationale. The current lack of exchange between HTD and European HTA bodies is a major point of concern. All HTD should be offered the opportunity of exchange with the European HTA bodies within the process of PICO consolidation.	
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)	19	3.4	Comment: We strongly agree with the authors that a fast, well thought-out, and binding solution is urgently needed to account for the risk of labelling change.	
Sallie Latimer, Lumanity	19	Section 3.4	Please provide clarity on when a solution will be proposed to account for the risk of labelling change (i) within EUnetHTA 21 and (ii) within the Regulation (EU) 2021/2282. Please also confirm that any proposed solution(s) will be made public for consultation prior to adoption. On face value, cooperation between the HTAR assessors and corresponding regulatory team could definitely contribute to a long-term solution and should be explored in preparation for the HTAR 'go live' in 2025. For example, a joint assessment of the risk of labelling change	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			could be conducted at each regulatory stop clock and where there is high risk, potential value of including more than one population option in the PICO scoping process should be considered to try and minimise the extent of delay to the evaluation process. Any proposed solution for consultation should provide detail on the additional steps and timings in the case of a labelling change at each step of the standard process.	
James Ryan, AZ	19	Section 3.4	Label changes are relatively infrequent (approx. 10 to 15%) and are usually a sub-set of the original trial population. It would be expected that through regular engagement during the process between the assessors, coordination group and the HTD, as well as concentrating on pre-specified sub-groups and usage of regulatory clock-stops, these should not usually impact on the report's draft publication as outlined in the Regulation. Where needed, and so as not to impact Member State timelines, complimentary analyses should be considered.	
GSK	19	347 table 3-8 last row 'O'	If different MS requested different outcomes, should one combine them and put them into every PICO?	
Matias Olsen, EUCOPE	19	347	Table 3-8: Consolidated PICOs based on Member States requests might need to refer to "I" as well, to specify e.g. different dosing in subpopulations, accounting for labels including adults/children).	
Silke Walleser Autiero Medtronic	19	347	Within the medical device field, a technology is commonly dependent on local patient pathways, meaning many different comparators can be relevant within and even more between member states. The proposed PICO approach therefore runs the risk of producing a fragmented, complex evaluation for many subgroups for which specific evidence might not be available at the time of assessment.	
James Ryan, AZ	19	347	PICO 1, 2 and 3 should be a single PICO with different comparators	
Mihai Rotaru - EFPIA	19	349	EFPIA proposes that, as part of the PICO validation phase, a scoping consultation/meeting should take place as a F2F or Online meeting including the HTD, to allow the HTD to ask clarifying questions, to explain its position and data availability and discuss the range of appropriate methodological analyses to assess the parameters included in the assessment scope. It would be helpful to ensure that (1) feedback from the HTD on any issues around feasibility of proposed PICO are provided (eg, that a particular comparator/population/outcome measure may not have enough patients available in the relevant studies to be able to provide statistically robust and meaningful information, thus additional data sources should be considered based on their added value, i.e. robustness	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			and evidence generation aspects), and (2) that due consideration is given to issues around multiplicity that this degree of disaggregation of clinical trial data that wasn't designed for this purpose may introduce. The validation process as described doesn't indicate direct consideration of issues such as multiplicity, statistical validity, and even patient privacy if this involves disaggregating data in such a way to go against existing standards (ie, less than 10 patients in a group).	
Tanja Podkonjak – Takeda Pharmaceuticals International AG	19	349	As suggested in the general comments, Takeda supports the proposal that, as part of the PICO validation phase, a scoping meeting should take place which would include the HTD. This would allow the HTD to ask clarifying questions, to explain its position and data availability and discuss the range of appropriate methodological analyses to assess the parameters included in the assessment scope.	
MTE	19	349	role of stakeholders is unclear: how long, how and what is the final weight of those stakeholders?	
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)	19	351	Comment: In view of the tight time constraints under the EU-HTA regulation and especially during EUnetHTA 21, precise deadlines are needed to create reliability and trust for all stakeholders. We recommend to strengthen the prioritisation of the potential PICO presentation timings, to ensure a smooth timeline of the PICO consolidation. Suggestion for rewording: *"This presentation should regularly take place during a programmed JCA CSCQ. If timelines dictate, it could also take place during a dedicated meeting."*	
M. Ermisch – GKV-Spitzenverband	19	352	Concerning timelines, we reiterate that timelines are yet unclear to us.	
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)	19	354	Comment: According to HTA Regulation (EU) 2021/2282 Article 8(6) sentence 4 "the scoping process shall also take into account […] input received from patients, clinical experts and other relevant experts". Input from affected patients and clinical experts for the disease in question is crucial to fully understand and cover the current standard of care and unmet need in an indication. Although not specified whether this input shall be gathered on national and/or EU-level, input from respective patients and clinical experts is needed from all MS since the standard	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			of care and unmet need can differ nationally. Furthermore, it is possible for MS to delegate the task of defining the required PICO parameters to their national HTA bodies, in which payers can make up a large proportion of the voting members (e.g., the G-BA in Germany). Hence, including affected patients and clinical experts in the scoping process on the national level could help to ensure that PICO requirements such as the comparator are not only selected due to economic considerations. In the present draft of the sub-deliverable D4.2 – Scoping Guideline "MS are encouraged to involve local patients and clinical experts to ensure that their inputs cover all their needs for a national evaluation" (page 9, lines 138-9) and "patients and clinical experts are invited to comment on consolidated PICOs" (page 19, lines 354-5). The current wording allows for the possibility that input from patients and clinical experts is not actively sought at either step of the scoping process. We recommend to rephrase at least one of the relevant passages, preferably both (cf. comment to page 9, line 138). Suggestion for rewording: "*[...] as well as patients and clinical experts in the respective therapeutic field will be asked to comment […]*"	
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)	19	355	Comment: Will the validation of the final PICOs by the CSCQ members be binding for all MS even if e.g., a MS was unexpectedly not represented at the respective CSCQ JCA meeting? If this is not the case, we recommend to include another iteration loop, in which all MS have to indicate whether the PICO they need is included in the consolidated PICO. Furthermore, we recommend to consider possible scenarios and define the consequences in case a consensus cannot be reached. In this case, it is imperative to avoid negative consequences (e.g., shorter timeline, additional national HTA) for the HTD. Suggestion for rewording: "*[…] a consensus must be reached that respects all MS requirements […]*"	
Dr Martin Danner BAG SELBSTHILFE	19	355	After "… the consolidated PICO's" should be added: "For the PICO's refer on the perspective of the different MS, patients an clinical experts of these MS should be involved."	
Sallie Latimer, Lumanity	19	Line 357	Please consider making the results of the PICO survey and consolidation tables available to the HTD as appendices to the validated PICOs that will be forwarded.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			In the absence of HTD inclusion in the scoping process, this will at least help the HTD explore any differences in the validated PICOs versus expectations of PICOs. It will also prevent duplication of PICO consultation by the HTD at the national level when considering local applicability needs.	
Tuomas Oravilahti, FIMEA	19	358	The final indication is likely to be limited from the suggested, rather than extended. This means that a short review round in MS should be enough to see if comparators or subgroups can be left out. Experiences from NICE could be helpful to hear when finding a solution for this issue.	
BIOTRONIK SE & Co. KG	19	359	The timelines proposed in MD assessments are not feasible and will not lead to a significant increase in insights. A later assessment would also prevent the uncertainty outlined in line 363; these will be commented on separately in comments on 4.7.1. Here the sentence in line 359 should be adjusted to 'Given the timelines of the JCA for pharmaceuticals, the scoping…'	
Dr. Thomas Ecker, Ecker + Ecker GmbH	19	354–355	**Statement in guideline:** *"CSCQ members as well as patients and clinical experts are invited to comment on the consolidated PICOs."* **Comment:** We welcome the participation of patients and clinical experts in defining the final assessment scope. However, we suggest that the following aspects, which so far have not been addressed, will be incorporated in the updated version of this guideline: • Which criteria apply for patients and clinical experts to be involved in the PICO consolidation? • How are patients and clinical experts informed about their possibility to take part in this process? How exactly will the input from patients and clinical experts be documented? Will this information be publicly available in order to ensure transparency of the process?	
Dr. Thomas Ecker, Ecker + Ecker	19	363–365	**Statement in guideline:** *"If CHMP opinion/CE marking recommends a different indication from the one initially applied*	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
GmbH			*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."* **Comment:** We do agree, that a detailed concept for handling of labelling changes has to be developed. At this moment, no timelines for this scenario have been defined, however, a concrete timeframe is essential to ensure high quality of the submitted data. Firstly, it is currently unclear what the timeframe is for updating the PICO schemes. Moreover, in this context, we would like to point out, that labelling changes and the resulting adaptions/changes in PICOs might require modified or even completely new data analyses. However, data analysis can be very time consuming (up to several weeks depending on the scope of these analyses). Moreover, the newly generated data then needs to be incorporated into the dossier, which also requires time. Will there be a defined mechanism of interaction between HTD, EMA and European HTA bodies to enable an early exchange between the involved stakeholders in case of labelling changes? Labelling changes might already be discussed at earlier timepoints in the regulatory process – in these scenarios, it will be essential, that these upcoming changes are communicated as soon as possible, especially if these changes result in modifications of the PICO schemes. Only in this way, it will be possible to adjust the dossier in a timely manner.	
Dr. Thomas Ecker, Ecker + Ecker GmbH	19	366–368	**Statement in guideline:** "*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."* **Comment:** We welcome the fact that a close cooperation between the regulatory team and assessors/co-assessors is envisaged. However, we are convinced that HTD should be involved in this exchange providing insight into the new medicinal product and its development in order to allow for a fruitful cooperation between the stakeholders involved in the European HTA	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			procedure.	
Matias Olsen, EUCOPE	20	371-374	Will the final PICO scheme that is communicated to HTD include information on the single PICO schemes defined by each Member State? This aspect is highly important in order to achieve a transparent process and to enable appropriate preparation for national HTAs. Therefore, the individual results of the PICO survey for each Member State, named appendix A (please also refer to p. 25 of this draft guideline), should be shared with HTD. What are the consequences if, after the PICO has been announced, it is already clear that the required evidence does not exist and therefore cannot be provided by the HTD?	
Matias Olsen, EUCOPE	20	371-374	If head-to-head evidence is not available, is an indirect comparison for each and every PICO required?	
Matias Olsen, EUCOPE	20	371-374	"Due to the high efforts for individually tailoring data and the potentially vast ramifications when providing incorrect data, the HTD should be given the opportunity to ask about the scope and parts of the PICO(s) that might have ambivalent or unclear meaning." Add: "**The HTD is given the opportunity to inquire about any unclear wording regarding PICO(s) whenever possible during the duration of the scoping process.**".	
Advanced Medical Services GmbH	20	372-374	When will the health technology developer (HTD) be informed about the timepoint of assessment scope finalization? Currently, only the consolidated and validated PICO / assessment scope will be forwarded to the HTD. We miss a step where the HTD will be informed prior to the final PICO / assessment scope. Thus, the HTD has no opportunity to prepare the submission template including required data analyses and to present evidence in a timely manner. The HTAR as well as EUnetHTA 21 do not consider a step that is quite important in the German HTA (AMNOG process) and decisive for its successful performance: the G-BA consultation of the HTD in order to discuss appropriate comparators and the evidence actually available as based on data collected in clinical studies.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Dr. Thomas Ecker, Ecker + Ecker GmbH	20	Section 4	**Comment:** Will the final PICO scheme that is communicated to HTD include information on the single PICO schemes defined by each member state? This aspect is highly important in order to achieve a transparent process and to enable appropriate preparation for national HTAs. Therefore, the individual results of the PICO survey for each member state, named appendix A (please also refer to p. 25 of this draft guideline), should be shared with HTD. What are the consequences if, after the PICO has been announced, it is already clear that the required evidence does not exist and therefore cannot be provided by the HTD?	
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)	20	4.0	Comment: The scope and presentation of information provided to the HTD is critical to enable the submission of a dossier fully meeting every MS needs. In the current draft it is unclear which information the HTD will receive and when, as Section 4.0 leaves many questions unanswered, both in terms of administration and content regarding the provision of information to the HTD. Among others: •When will the information be provided to the HTD? The deadline should be the same in all processes, i.e., already defined, and also as early as possible to enable the submission of a complete dossier for evaluation. We recommend to define the deadline for communication to the HTD and to include it into this section (cf. comment to page 10, Figure 3-1, step 9). •Will the HTD be informed about the original MS PICO requests as well as the consolidated minimal number of required PICOs? E.g., to enable the submission of a dossier containing the best available evidence, the HTD needs to be informed about all potential "OR" comparators for all MS. Preferred comparators i.e., comparators that are required by further MS could be highlighted. We strongly recommend to inform the HTD about all potential "OR" comparators (cf. comment to page 16, section 3.2.3). •Will the HTD be informed which PICO was requested by which MS and how often each PICO was requested? In view of the tight timelines and anticipated shortage of JSCs, we strongly recommend to communicate these information to the HTD. This way, in the case of limited resources the HTD could prioritise for additional post-hoc analyses during the small window of time between informing the HTD about	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			requested PICO(s) and the submission deadline of the HTA submission dossier. It would also help the HTD to adapt for the MS-specific policies. •Will there be one general way to analyse and present the required data or will different MS be allowed to request different types of analyses, e.g., certain effect estimates or set different thresholds for minimal important differences of response rates? In the current draft, the statistical requirements for data presentation in the HTA submission dossier remain unclear. It is also not specified when and in which context those requirements will be communicated to the HTD. We recommend to either include this information in the draft or refer to the sub-deliverable which will specify the statistical requirements. •What will be the consequences of an incomplete dossier? If, for example, a PICO or additional information such as certain subgroup-analyses are missing for one PICO, but other requested PICOs are fully met, will the dossier as a whole not be evaluated or only the section in question? We recommend that the exact consequences of different extents of missing information be determined in advance. If this is not in the scope of this sub-deliverable, we suggest referencing the appropriate sub-deliverable. Overall, we recommend to elaborate this section and to specify the timing, content and presentation of the information for the HTD.	
Roche	20	374/4	Once defined after the PICO survey, the PICO should not be changed during assessment, unless label indication changes or evidence-driven justification is provided to the HTD. Any changes made by EUnetHTA to the PICO during the assessment should be discussed with the HTD. Additionally, the HTD should be able to suggest changes to the PICO based on changes in the treatment paradigm. Necessary changes can take place at national level based on the indication statement.	
Norbert Gerbsch for IGES Institut GmbH and HealthEcon AG	20	371-374 / 4	**Comment:** REGULATION (EU) 2021/2282 Art. 8 (7) and Art. 10 (1) provide a chain of information to the HTD for the official decision about the assessment scope and request the submission oft he dossier. The regulation however does not forbid to give HTDs the opportunity to be involved especially to avoid possible misunderstandings. Due to the great efforts for individually tailoring data and the potentially vast ramifications when providing incorrect data due to misunderstandings or misinterpretations, the HTD should be given the opportunity to ask about the scope and parts of the PICO(s) that might have ambivalent or unclear meaning.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			Suggestion: Add in line 273: "The HTD is given the opportunity to inquire about any unclear wording regarding PICO(s) whenever possible during the whole scoping process".	
Mihai Rotaru - EFPIA	20	371	Beyond the final assessment scope, the divergent recommendations and input gathered during the PICO survey by the countries should be made visible to the HTD to allow to prepare for potential complementary (unavoidable) request and submissions (predictability both for HTD and MS).	
–Tanja Podkonjak – Takeda Pharmaceuticals International AG	20	371	Beyond the final assessment scope, Takeda requests the responses of individual MS PICO survey, and their accompanying rationale, be made visible to the HTD to allow to prepare for potential complimentary request and local submissions.	
Dr. Thomas Ecker, Ecker + Ecker GmbH	9–12	Section 3	**Comment:** While on level of each member state, the PICO is defined according to standards of evidence-based medicine and national policies, no clear rules are defined for determining the final PICO schemes for the joint HTA. From our point of view, a methodology for defining the assessment scope has to be established including principles for choosing comparators and dealing with multiple PICO requests. Based on these criteria, assessors and co-assessors should then define a core set of PICO schemes representing the overall assessment scope. Thus, we propose the following criteria for deriving the PICO scheme. Population: • The patient population should be defined in accordance with the (draft) SmPC. • A maximum choice of subpopulations should be defined. Requests for subpopulations have to be derived from a medical rationale. Intervention:	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			• The intervention should be defined in accordance with the (draft) SmPC. Comparator: Regarding the criteria for determining a comparator, an approach focusing on medical evidence is necessary. Therefore, from our point of you, an approach similar to the process applied by the Federal Joint Committee (G-BA) in Germany could prove to be purposeful. According to the criteria determined in chapter 5, section 6 of the rules of procedure of the G-BA, the appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally accepted state of medical knowledge, preferably a therapy for which endpoint studies are available and which has proven its worth in practical application. Based on these considerations, we propose the following criteria: • When the comparator is a medicinal product, it must have a marketing authorisation for that indication and line of treatment. • Pharmaceutical compounds that are used off-label should not be considered as comparators. • There must be procedures for resolving the issue of multiple comparator requests from the member states (especially in cases, where all listed comparators are required, so called "AND" situation). A maximum choice of comparators should be defined. The comparator should be determined based on international standards of evidence-based medicine (e. g. based on clinical guidelines). The comparator should represent the current state of medical knowledge.	
BIOTRONIK SE & Co. KG	21	Figure 5-1	'Relevant studies named' to be removed from the graphic to be outlined for each PICO. Exploration of relevant existing evidence should remain part of the assessment and be kept separate from scoping, as is current practice.	
James Ryan, AZ	21	Section 5	Should this section of report template be included in the guidance? Is it more appropriate for D5.1 and D5.2 in the EUnetHTA 21 work programme (we presume this is what is referred to as the EUnetHTA template in line 403)?	
Tuomas	21	375	This chapter seems to be in a wrong guideline.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Oravilahti, FIMEA				
Roche	22		A statement should be included around the acceptance and use of indirect treatment comparison (methods defined by WP D4.3.2) to enable the comparison of study data to the developed PICO(s).	
GSK	22	412-415	Does one need to assess the degree of deviation?	
Silke Walleser Autiero Medtronic	22	412-415	Adaptation of the statistical analysis plan according to the specific PICOs implies two questions: 1. Feasibility for the HTD to be able to do that and still submit a dossier in 45 days Methodological implications: for example, are HTD permitted to conduct and submit sub-group analysis if they have not been planned in the protocol? Usually, this type of ad hoc analyses have been refused by the Medical Device Commission of the HAS in France.	
Tanja Podkonjak – Takeda Pharmaceuticals International AG	Page 22	412-415	The current Scoping Guideline states: "To meet the data requirements for an assessment according to a specific PICO, the available studies might need to be reanalysed 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 r-analyses will be provided by the HTD in the submission dossier." Takeda is concerned that unless individual patient-level data (IPD) are available for the studies evaluating the comparators, it would not be possible to conduct this re-analysis. In most cases, re-analyses are possible only for the study evaluating the intervention. Takeda requests that the Scoping Guideline explicitly acknowledge this situation. In addition, we request the Scoping Guideline detail what information should be provided in the submission dossier if re-analyses of the study data the intervention (or comparator data should IPD be available) are conducted. Takeda respectfully requests that either: 1. The Scoping Guideline document explicitly states what information is expected from HTDs in the situation that reanalyses are needed, or 2. That the Scoping Guideline in Section 6 explicitly states that guidance on what information is expected from HTDs in the situation that reanalyses are needed will form part of the forthcoming JCA template. In this situation and to avoid confusion, we recommend	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			the JCA template be subsequently included as an appendix to the Scoping Guideline. This can help standardize the information included by HTDs in the submission dossiers and ensures that the HTDs will include the expected information from the JCA assessors.	
Matias Olsen, EUCOPE	22	407-408	PICOs should be based on evidence based medicine and preferably European treatment guidelines, in exceptional circumstances national guidelines. Add: "As described above, the PICOs are developed based on the national questions to be answered by the assessment**, which are to be informed by evidence based medicine**".	
Matias Olsen, EUCOPE	22	417-418	This phrase needs to be further specified. In what form will the original study analyses be part of the dossier – for example, in the form of the clinical study report (CSR) attached to the dossier (comparable to the unpublished Module 5 of the German dossier) or as analyses depicted in a chapter of the submission dossier? There could be cases where the original study analyses do not cover the defined PICO schemes.	
Norbert Gerbsch for IGES Institut GmbH and HealthEcon AG	22	418 / 6	**Comment:** „In any case, the original study analyses will be included in the dossier." Therefore they should also be included in the HTA report. **Suggestion:** Change line 417 to: „In any case, the original study analyses will be included in the dossier and the HTA report".	
Roche	22	414-418/6	The strengths and limitations of endpoint types (primary, secondary, exploratory) should be acknowledged in the assessment report. Furthermore, statistical testing should not be required for post-hoc analyses as they are exploratory in nature and provide estimates rather than statistical tests. Suggestion for rewording for clarity: *"This analysis will deviate from the original study **~~planning~~ planned analyses** but it is **~~required~~ critical** for the **~~HTA~~ joint clinical assessment** by the definition of the PICO**(s)**. **~~This~~ Such** deviation**s** should be clearly mentioned **in the HTD***	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			submission dossier and the JCA report. Statistical testing is not required for reanalyses, as these are "exploratory" in nature and provide estimates rather than statistical tests. ***[…]*** *In the assessment report, it should be clear which data sets are from analysis according to the original study planning and which are based on reanalysis resulting from PICO requests,* ***as well as it should acknowledge strengths and limitations of each type of analysis and endpoints types (primary, secondary, exploratory)****. In any case,* ~~***the***~~ *original study analyses* ***which address the PICO requests****, will be included in the dossier."*	
Tuomas Oravilahti, FIMEA	22	404	This chapter seems to be in a wrong guideline.	
BIOTRONIK SE & Co. KG	22	412ff	This paragraph implies that post-hoc analyses and indirect comparisons are now basic acceptable practices and are comparable to direct study data to accommodate the breadth of the intended assessments. This should be clarified in the methods.	
Mihai Rotaru - EFPIA	22	413	To meet the data requirements for an assessment according to a specific PICO, it should be made clear that re analysis of the clinical trial might not be enough, the HTD might have to perform an indirect comparison. The link to the current public consultation (direct and indirect comparison) should be added. In some cases, it may not be possible, from a methodological point of view, to answer to the data requirement for a given PICOs.	
EFSPI	22	413	There should be some guidance on scope of re-analysis vs original SAP (or a reference to the appropriate guidance document detailing this). For example, the typical CSR SAP will specify analyses for multiple estimands for key endpoints. Are these all to be repeated on subpopulations of interest for the JCA? Or just some of them (which ones)? Generally, not only the SAP, but also the study design require consideration for addressing whether one or more PICO can be appropriately addressed in the studies available. The consolidation process should account for scientific and statistical considerations (multiplicity, scientific relevance, etc)	
James Ryan, AZ	22	415	Typo: r-analyses should be reanalyses?	Y
BIOTRONIK SE & Co. KG	22	417f	Please clarify whether all studies should always be included even if they are irrelevant to any of the PICO. Given the breadth of the intended assessments this is a true possibility.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
James Ryan, AZ	22	417	Should this provision of analyses be included in the guidance? Is it more appropriate for D5.1 and D5.2 in the EUnetHTA 21 work programme? Recommend the following addition: "In any case, the original study analyses **applicable to the European joint clinical assessment** will be included in the dossier" This ensures that only those analyses relevant to the policy formed PICOs are included, ensuring a timely and high-quality submission and assessment report.	
Prof. Matthias P. Schönermark, M.D., Ph.D. and Svenja Sake, Ph.D. (SKC)	22	418	Comment: The selection of relevant outcomes needed by individual MS is part of the PICO survey. Subsequently, the PICOs including the requested outcomes will be consolidated to minimal amount of data needed for the HTA. In this light it is not entirely clear whether "[…] the original study analyses will be included in the dossier" concerns all endpoints included in the respective study/studies, e.g., exploratory and/or non-patient-relevant endpoints. Do those data have to be presented and discussed in all cases, is the presentation of some data, especially of surrogate data, in an annex possible? We recommend to further elaborate or specify the request for original study analyses.	
Sallie Latimer, Lumanity	22	Line 418	Please confirm that the original study analyses should be included in the dossier, even in the case that they are not directly relevant to any of the final PICOs. For example, where the regulatory application is based on subpopulation analyses rather than full population analyses.	
Dr. Thomas Ecker, Ecker + Ecker GmbH	22	417–418	**Statement in guideline:** "*In any case, the original study analyses will be included in the dossier.*" **Comment:** In our opinion, this phrase should be specified. In what form will the original study analyses be part of the dossier – for example, in the form of the clinical study report (CSR) attached to the dossier (comparable to the unpublished Module 5 of the German dossier) or as analyses	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			depicted in a chapter of the submission dossier? There could be cases where the original study analyses do not cover the defined PICO schemes.	
Dr. Thomas Ecker, Ecker + Ecker GmbH	11, 12	178, 222	**Comment:** A maximum number of subpopulations should be defined. Requests for subpopulations should be based on a medical rationale. Moreover, currently, it is unclear, whether subgroup analyses will be requested in the dossier template. In case subgroup analyses are regularly requested for the submission dossier (e. g. if applicable for age, gender, severity/stage of the disease, regional effects – an approach established in the German benefit assessment), no additional subpopulations should be defined as part of the PICO scheme. Furthermore, no additional requests for analyses of potential effect modifiers, which have been raised by single member states, should be considered. Due to the short timeframe between definition of PICO schemes and dossier submission, a predictable framework for required analyses is essential to deliver analyses within this short time period.	
Dr. Thomas Ecker, Ecker + Ecker GmbH	11, 12	195–199, 223–229	**Statement in guideline:** "*In rare occasions, this background therapy might differ from one MS to another. 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.*" "*MS could specify background-associated treatment (pharmacological or not) to be added with the evaluated intervention (e.g., psychotherapy as a background therapy with an antidepressant medicinal product; a diet with an antidiabetic medicinal product; physiotherapy as a background therapy for an orthopaedic spine device, etc.) to highlight specific national care approaches. MS are expected to consider the role of background treatments carefully, because they might belong to one of the PICO elements, such as the*	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			comparator. MS should provide a clear rationale for why the background therapy is not among the PICO elements." **Comment:** Since the issue with a specific background therapy might be raised more often than currently assumed, the guideline should state clear criteria for inclusion of a specific background therapy as part of the intervention. How should different standards of care be dealt with? If a background therapy is not named as part of the comparator but is instead listed under "additional information", is the PICO scheme still considered fulfilled if the comparator was correctly implemented in the study but the background treatment therapy listed under "additional information" was not incorporated into the study design? In brief, what are the requirements for the evidence needed in case a background treatment is defined under "additional information"?	
Paolo Morgese - ARM	24	422-435	While this section is helpful in clarifying that the D4.2 mainly applies to EUnetHTA 21 and only to some extent to the HTAR, it raises questions on the utility of setting up a Scoping Process that would possibly not work for the JCA. As several of ARM comments underline, the D4.2 guideline looks overambitious in allowing a large number of selected PICOs. D4.2 also states that the Scoping Process should be based on information available at time of the JCA submission, including the PICO survey with MS. ARM expects D4.2 to be more pragmatic, setting realistic objectives in terms of comparators (and PICOs) and outlining in more detail a feasible process.	
Advanced Medical Services GmbH	24	422-433	Provide an overview table with columns as follows: • HTAR as basis, refer to Article and paragraph. • Content applicable to both EUnetHTA 21 and HTAR. • Indicate deviation in EUnetHTA 21 process step, specify differences and changes from EUnetHTA 21 to HTAR. • Relevant functions in EUnetHTA 21 only. • Final solution for HTAR following EUnetHTA 21 interim phase. Indicate corresponding committees and other institutions (e.g. Commission), and their respective tasks in each process step.	

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Advanced Medical Services GmbH	24	434-435	HTAR, Article 8(6), last sentence: "The scoping process shall also take into account information provided by the health technology developer and input received from patients, clinical experts and other relevant experts." Proposal for D4.2: "Input from patient organisations or clinical experts as well as information provided by the health technology developer should be considered in the future in relation to implementing the HTAR." In addition, refer to HTAR: Article 29(3) lists HTD as eligible candidates to become part of the stakeholder network.	
Sallie Latimer, Lumanity	24	Section 8	Please consider explicitly listing differences in EUnetHTA 21 and the HTAR and what is meant by "the scope of this guideline is limited to the relevant functions in EUnetHTA21" – this seems contradictory to the "much of the content of this document is applicable to both EUnetHTA 21 and the HTAR" statement in the same paragraph. Please confirm when details of how the scoping process will be started and how information on the intervention and the indication will be requested in the HTAR will be made available and if they will be released for consultation prior to adoption.	
Roche	24	434-435/8	Not only input from patient organization or clinical experts should be considered in the future in relation to implementing the HTAR. The input of the HTD should also be taken into account/considered. Suggestion for rewording: "Input from patient organizations, clinical experts, **and HTDs** should be considered in the future in relation to implementing the HTAR."	
Sallie Latimer, Lumanity	25	Appendix A	Please consider including a completed example of the PICO within the PICO survey form and piloting the PICO survey form prior to use to check MS understanding of the requested information versus guidance.	

<table>
<tr><th>Comment from</th><th>Page</th><th>Line/ section number</th><th>Comment and suggestion for rewording</th><th>Editorial comment?</th></tr>
<tr><td>Tanja Podkonjak – Takeda Pharmaceuticals International AG</td><td>Page 25</td><td>Appendix A PICO SURVEY FORM</td><td>Takeda recommends that the PICO SURVEY FORM include a RATIONALE column for each component of the PICO in the MS survey.

This will increase the transparency, efficiency, and for the assessor and co-assessor when consolidating the PICOs and provide clarity for the HTDs and patient and clinical experts in why a specific comparator, subpopulation, outcome, etc., is being requested in a PICO.</td><td></td></tr>
<tr><td>Dr. Thomas Ecker, Ecker + Ecker GmbH</td><td>12–19</td><td>Section 3.2</td><td>Comment:

Are the results of the PICO consolidation, which are shared with the HTD, published transparently including the results of the individual member states? The requirements stated from the individual member states are crucial for the national HTA process as well as for pricing and reimbursement.</td><td></td></tr>
<tr><td>Dr. Thomas Ecker, Ecker + Ecker GmbH</td><td>12–19</td><td>Section 3.2</td><td>Comment:

In the current consolidation process, the decision for the final PICO schemes is solely driven by majority: if the majority of countries requests a certain comparator, this comparator will be selected. However, this decision should be based on current medical knowledge.

Moreover, in the draft guideline, handling of the following scenario is not discussed:

Table 4: Exemplary list of submitted comparators

<table>
<tr><th>Member State 1</th><th>Member State 2</th><th>Member State 3</th></tr>
<tr><td>Comparator(s)

Could use any of ~~or all required~~</td><td>Comparator(s)

Could use any of ~~or all required~~</td><td>Comparator(s)

Could use any of ~~or all required~~</td></tr>
<tr><td>Comparator 1</td><td>Comparator 1</td><td>Comparator 1</td></tr>
<tr><td>Comparator 2</td><td>Comparator 2</td><td>-</td></tr>
</table>

In the scenario depicted in table 4 comparator 1 would be selected as comparator of the resulting PICO scheme. However, first of all, this approach does not take into account whether</td><td></td></tr>
</table>

Comment from	Page	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			comparator 2 might represent the more suitable treatment from a medical, evidence-based point of view (e. g. this treatment is recommended in recent clinical practice guidelines as new gold standard due to superiority, whereas comparator 1 might reflect a well-established treatment but is inferior to comparator 2). Therefore, this approach might result in favoring outdated treatment options. Secondly, in the current draft guideline, it is not specified, whether, in cases, where only evidence for comparator 2 is available, this evidence will still be considered for the assessment (in our example for the assessment of member state 1 and member state 2). For this reason, the availability of evidence should be considered in the consolidation process. Otherwise, this approach would result in loss of information rather than providing the best available evidence. In conclusion, the consolidation of PICO schemes should be driven by current medical knowledge. In particular, the choice of comparator should be based on available clinical evidence.	
Matias Olsen, EUCOPE	110	179	To ensure transparency and to avoid misunderstandings that might lead to inconclusive data presentations in the JCA, a comprehensive justification for the definitions of any subpopulations requested by the MS should be provided. Add: "The definition of the relevant population(s) should be as clear as possible and avoid ambiguity. **A comprehensive justification regarding the formation and definition of subpopulations will be provided.**".	

Comment from **The below comments were submitted after the deadline**	Page number	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Eurordis	6	78-80	"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" A crucial aspect of the European scoping is the synthesis of different perspectives by means of the	

Comment from The below comments were submitted after the deadline	Page number	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			discussion among partners. We suggest the w ording: "In the context of a European HTA, the assessment scope reflects a synthesis of policy questions from different healthcare systems, elaborated from a common European standpoint" The follow ing elements should also be part of that definition: • A direct interaction w ith health technology developer during the process is necessary to the best definition of the PICO questions and data requirements •The input from patient and clinical experts is also essential to elaborate relevant PICO questions	
	6	93-35	"Rather, an appropriate translation of national policy questions into research questions is performed during the planning stage of the assessment" We suggest the follow ing w ording change: "Rather, an appropriate translation ***and synthesis*** of national policy questions into research questions is performed during the planning stage of the assessment" The comprehensiveness of the scoping (Article 8.6 Reg 2282-2021) is not in contradiction w ith the necessary synthesis of Member States' needs, in order to elaborate an effective and viable PICO for the health developer submission.	
Eurordis	6	109-113	About PICO survey It is not clear w hether the PICO survey is completed/submitted by each HTA body w hich is part of the JCA subgroup or on a Member States basis. (Is it one PICO per HTA body or one PICO per country?)	
Eurordis	9	141-146	"The questionnaire for the PICO survey takes into account information provided by the HTD [Article 8(6)]…"	

Comment from The below comments were submitted after the deadline	Page number	Line/ section number	Comment and suggestion for rewording	Editorial comment?
			Remarks: 1. According to Article 8.6 of Reg 2282-2021, the first HTD submission will occur upon European Commission request and based on the PICO. 2. This quote seems therefore in contrast with the process describe in these lines 3. We understand these guidelines refers to EUnetHTA21 only when mentioning Letter of Intent and regulatory information to be provided in there by HTD 4. If these guidelines are supposed to refers to the future European HTA Cooperation (Reg 2282-2021), please, precise whether the authors foresee – in the new framework - an exchange of information at the initiation of the scoping process, either with HTD or with Regulators	
Eurordis	General		1. Reg 2282-2021 set the deadline for industry submission 45 days prior to expected CHMP option (Art. 10.1) 2. Therefore, we understand that the scoping phase, initiated by the subgroup (Art 8.6), should start far in advance 3. That means that exchange with Regulators and/or HTD should occur at the time of the initiation of the scoping Hypothesis about the timing of the scoping initiation: The duration of the scoping process during EUnetHTA JA3 for PT was on an average of 180 days / 5,5 months. At the end of JA3 that average was 4 months. For PT, preliminary reports from CHMP rapporteurs are due at day 60 an at day 120 of the EMA procedure. Initiating the scoping for PT based on the day-120-CHMP-report would mean leaving less than 60 days (in not accelerated procedures) to complete the scoping before the Art 10.1 deadline for industry submission (less than 2 months). We suggest: 1. To precise the timing and the actual steps of the scoping initiation/kick-off wherever	

Comment from The below comments were submitted after the deadline	**Page number**	**Line/ section number**	**Comment and suggestion for rewording**	**Editorial comment?**
			possible, though that information might be only indicative. 2. To envisage the possibility to initiate the scoping for PT in correspondence with the day-60-CHMP-report.	
Eurordis	9	147-148	"The MS will be made aware of any Joint Scientific Consultation (JSC) that might have taken place for the medicinal product or MD under discussion". We fully endorse this point	
Eurordis	10	Figure3-1	We suggest including the step of discussion with the manufacturer, at the stage of PICO consolidation, which should also include the participation of patients and clinical experts. The discussion with HTD is crucial to enable the HTD to submit a viable dossier that meet the PICO requirements. The participation of patient and clinical experts is crucial to assess the relevance of the questions, especially the outcome	
Eurordis	11	205-206	"Comparator(s) could be approved or not (off-label) in the European Union (EU)". We suggest the wording: "Comparator(s) should be products approved in the EU. Those could be approved for a different indication (off-label) than the one of the technology under assessment".	
Eurordis	12	232-242	Section 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).	

Comment from The below comments were submitted after the deadline	**Page number**	**Line/ section number**	**Comment and suggestion for rewording**	**Editorial comment?**
			The PICO consolidation phase requires the assessment team to discuss with the HTD in a dedicated meeting, with patient and clinical experts whenever possible. To achieve the fewest PICO(s) possible during the consolidation phase, the assessor and co-assessor might contact to clarify open questions resulting from the PICO survey and discuss options for consolidation. *The objective of the consolidation is to ensure that all 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 medicinal product), and at least one outcome. The steps are explained below and are illustrated with an example*".	
Eurordis	18	Figure 3-2	We suggest including in this Figure: - the discussion with the HTD (see previous comments) - the PICO validation step The PICO validation shall be the moment where MS, patients and clinicians make a synthesis of all the questions and endorse the final PICO.	
Eurordis	19	355-356	The PICO validation should be a moment of discussion and synthesis, with MS and patients and clinicians. That cannot be an automatic endorsement of the PICO consolidation. Otherwise, there is no European added value in the process. Therefore, we suggest deleting the following sentence: "However, a consensus should be reached that respects all MS requirements because this requirement is determined by Article 8(6). CSCQ members should validate the final	

Comment from The below comments were submitted after the deadline	**Page number**	**Line/ section number**	**Comment and suggestion for rewording**	**Editorial comment?**
			PICOs. And substituting it with: CSCQ members as well as patients and clinical experts are invited to comment ***and discuss*** on the consolidated PICOs. CSCQ members should validate the final PICO. ***The PICO validation outcome should be as inclusive as possible (as per art 8.6) and endorsed by MS***." We also suggest highlighting the importance of the engagement of patient and clinical experts at the European stage, by including the following wording: "For the whole process to be trust, witnesses are needed. Civil society representatives such as patients and clinicians meet the principle of publicity and transparency in HTA. Furthermore, the participation of patient and clinical experts is meant to ensure the highest quality of the HTA process and the relevance of the PICO questions. In addition to national engagement at the PICO survey stage, engagement of patients and clinicians at the European stage will improve the capability of all countries/assessors with no distinction, improving the added value of the European cooperation."	
Eurordis	20	371-374	We don't endorse the absence of any discussion with the HTD, and the limitation of the interaction to the information about the final PICO. The PICO survey or the consolidated PICO shall be discussed in a meeting between the assessment team and the HTD.	
Eurordis	22	404-418	We suggest including the following: Potential misalignments between HTA requirements and the development should tentatively be discussed at the stage of JSCs.	

Comment from The below comments were submitted after the deadline	**Page number**	**Line/ section number**	**Comment and suggestion for rewording**	**Editorial comment?**
			Misalignments that arise at the scoping stage between the PICO survey or the Consolidated PICO and the available studies, should be discussed in a dedicated scoping meeting with HTD, considering the advice given in JSC and the reason behind any deviation.	
Eurordis	24		About chapter 8 Considerations for HTA Regulation We suggest move this disclaimer at the top of the document.	x

Comments received outside EU/EEA countries without a direct link to the HTAR

Name organisation & abbreviation	Country
College of Pharmaceutical sciences, Dayananda sagar university	India
PHMR Limited	UK

Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Editorial comment?
Dr K V Ramanath, Dayananda Sagar university	General	--	The entire document is written correctly	---
Frauke Becker PHMR	General		The role and involvement of the assessor/co-assessor needs to be clearer. Is their role more administrative-focussed to consolidate all evidence, i.e. do they form the link between HTD and member states, or do they also have a main part in the assessment from a technical angle?	
Frauke Becker PHMR	22	6	The process around re-analysis of data to fit requirements for an assessment according to a specific PICO is not clear. If re-analyses are required that differ from the originally planned analyses (as specified in the statistical analysis plan), it would require additional inputs (that were not planned for) and could have substantial impact on project timelines. How much time will be given to submit updated analyses that fit requirements of the PICO? How will the results from different analyses be considered in the assessment? Will the originally planned analyses be considered at all?	