Comments on EUnetHTA 21's D4.2 – Scoping Process – Practical Guideline

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 ATMPs 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.

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.

Page number	Line/ section number	Comment and suggestion for rewording
General	-	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

The guideline is available here:
Scoping Process Practical Guideline

Ecker + Ecker GmbH
Warburgstr. 50
20354 Hamburg
www.ecker-ecker.de

		• **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 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.

Comments on timelines		
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? 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.
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?
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.
19	363–365	**Statement in guideline:** “*If CHMP opinion/CE marking recommends a different indication from the one initially applied for, an update of the PICOs is expected and the evaluation process will be delayed. A solution is needed to account for the risk of labelling change.”* **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.

Comments on involvement of Health Technology Developers (HTD)		
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.
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?
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 procedure.

Comments on PICO survey & consolidation		
6	92–95	**Statement in guideline:** „*By principle, the scope of the assessment of an intervention should not be data driven, that is, the research questions should not be deduced from the available studies. Rather, an appropriate translation of national policy questions into research questions is performed during the planning stage of the assessment*." **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.
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.
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: • 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.
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.
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)*"
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 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"?

<table>
<tr>
<td>11</td>
<td>209</td>
<td>Statement in guideline:

“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.</td>
</tr>
<tr>
<td>11</td>
<td>206–208</td>
<td>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’ […].”

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 1 and table 2 below).

Table 1: 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 1 would all medicinal products (A–E) be included as comparators in the resulting PICO scheme?</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>
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: 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 table 2 result in two distinct PICO schemes?
</td>
</tr>
<tr>
<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 3: 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 3 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 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.
</td>
</tr>
</table>

		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.
Comments on transparency of the process		
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?
12	215–219	**Comment:** With regard to the national HTA, it would be helpful to know which member states requested which endpoints.
12–19	Section 3.2	**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.
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?
Further comments		
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:** 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?

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:** 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?
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 depicted in a chapter of the submission dossier? There could be cases where the original study analyses do not cover the defined PICO schemes.