Comments on EUnetHTA 21 Public Consultation of D4.5 Applicability of evidence D4.6 Validity of Clinical studies D5.1 Guidance for JCA Submission Dossier Template

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.

On July 4th, the EUnetHTA 21 drafts deliverable “D4.5 Applicability of Evidence”, “D4.6 Validity of Clinical Studies” and “D5.1 JCA Submission Dossier Template” were published and are now available for public consultation.

Page number	Line/ section number	Comment and suggestion for rewording
D4.5 Applicability of evidence		
General	-	Some points, especially in the JCA requirement boxes, are repeated numerous times. A more compact structure with one summarizing box containing all general requirements at the end of the introductory section of a chapter could be helpful for the overall readability.
General	-	The requirements need to be specified unambiguously, so that the HTD can submit all necessary data and evidence. The draft guideline does not meet this need, as it is vague at multiple points, especially: • It is unclear, which subgroup analyses have to be submitted (only for a priori planned endpoints or for every endpoint). • It is unclear, which measures in particular are meant in the JCA requirement boxes e.g., `appropriate measures for statistical precision´. Subjective und ambiguous clauses such as `appropriate´ should not be used.

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		• It is unclear, if estimands should be used outside of the concept of sensitivity analyses. This should be stated explicitly.
12-13	3.2	In chapter 3, the topics of multiple operations and multiple effect measures are missing. As this is problematic in individual studies it should be mentioned. A possible solution would be a separate subsection analogue to chapter 4.
13	362-367	**Statement in the guideline:** *"Prespecification of subgroups is being encouraged in the planning of individual clinical studies as it can lend credibility to positive or negative subgroup findings. However, a priori planned subgroup analyses are often limited to the primary endpoint. From the perspective of assessment of an individual clinical study, all other subgroup analyses, such as analyses of subgroups or subgroup analyses for further endpoints not prespecified in the SAP, are unplanned analyses. These are not controlled for multiple hypothesis testing and lack statistical robustness."* **Comment:** We agree that evidence of unplanned subgroup analyses is limited. However, the text should be more specific about the consequences, especially whether unplanned subgroup analyses will be considered at all. If yes, clear criteria as to when unplanned subgroup analyses will be considered should be given.
D4.6 Validity of clinical studies		
General	-	Even if the scope of the guideline is the definition, classification and evaluation of certainty of study results, we would like to point out the necessity of clear guidance on the scope of evidence to be presented. Clear guidelines are required to ensure that all necessary data are presented.
6	137-140	**Statement in guideline:** *"Nevertheless, there might be justification to not assess the evidence that ranges below a minimum level of internal validity, applicability, or statistical precision in detail, if the PICO question can be sufficiently answered on the basis of higher-certainty results."* **Comment:** The term `minimum level of internal validity, applicability, and statistical precision´ is unspecific and therefore unclear. A concrete threshold for the `minimum level´ should be given, since otherwise evidence could be systematically excluded. We would like to point out that single arm studies as well can contribute valuable evidence.

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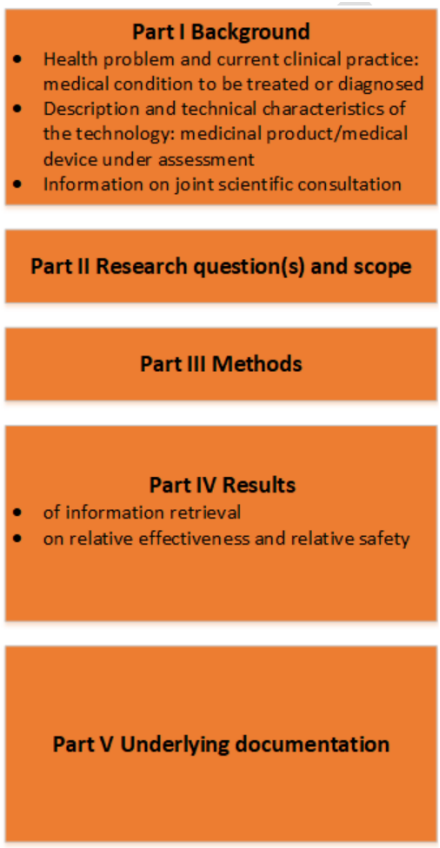
6	162/163	The reference is unclear. Documents should always be specified in a clear and unambiguous way.
8	222-224	**Statement in guideline:** *"Similarly, the clinical relevance of an effect size, which can be assessed by comparing the effect size with a predefined threshold or by responder analyses (25), needs to be judged at the national context."* **Comment:** Clinical relevance is commonly evaluated using minimal clinical important differences (MCID). MCIDs are an internationally accepted concept and are chosen on a scientific research basis and validated using established methods, such as anchor-based methods in a therapeutic area. The guideline should mention and encourage the use of established MCIDs. Furthermore, criteria should be given regarding when an MCID is considered valid and will be used. The concept of MCID is independent from the national context. It should be mentioned in this guideline or at least in the EUnetHTA Practical Guideline Endpoints.
8	230-233	**Statement in guideline:** *"For effect sizes expressed as relative risks, the threshold of a relative risk superior to 5 (or inferior to 0.2) and a p value <0.01 (as an indicator of sufficient precision) was proposed as a '* *rule of thumb' (i.e., an arbitrary rule based on expert opinion) (26,30)."* **Comment:** The guideline should not contain 'rules of thumb'.
D5.1 Guidance for JCA Submission Dossier Template		
General	-	Guideline D5.1 establishes an overall framework for the Dossier submission. However, currently no dossier template is available to reference to. We express our concern regarding the specific implementation of the guideline into the dossier template. A timely publication of the updated dossier template and subsequent revision process is required. • Three main concerns with regard to deliverable D5.1 – Submission Dossier Guidance are summarized below: • The information submitted by the health technology developer as appendices must be treated as strictly confidential. • Information on the regulatory status outside Europe is not relevant for the European HTA-process • Information on joint clinical assessments outside Europe is not relevant for the European HTA-process and information

		required on clinical assessments in Europe must be specified more clearly
7	85	***Figure 1 in guideline:***  **Figure 1. High-level structure of the dossier.**
22-24	466-535	***Appendix B-C*** **Comment:** The required underlying documentation in Part V of the HTA dossier includes highly confidential information for example "*all up-to-date published and* ***unpublished*** *information, data, analyses and other evidence as well as study reports and study protocols and analysis plans from studies […]* (Annex I (b) of the EU regulation 2021/2282) While transparency of the assessment process is important, protection of the confidential property by the health technology developer must be ensured during the entire assessment process. Information submitted as appendices must therefore be treated as strictly confidential. Please include a statement on the confidential nature of attachments to the submission dossier, referencing on Guideline D7.1.3 – Guidance for handling commercially in-confidence data.

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14	277	**Statement in guideline:** *An overview of the regulatory status outside Europe should be provided.* **Comment:** Information on the regulatory status of the health technology in countries outside of EU is not relevant for the HTA process in Europe. **Suggestion for rewording:** ~~An overview of the regulatory status outside Europe should be provided.~~
22	488-489	**Statement in guideline:** *If HTA reports from earlier joint clinical assessments or from other jurisdictions are available, these should be included.* **Comment:** Please specify that the term "earlier joint assessments", used in the Submission Dossier Guidance, refers to earlier joint assessments of the **medicinal product under evaluation in the indication under evaluation.** Furthermore, submission of clinical assessment of "other jurisdictions" are not mentioned in the EU regulation 2021/2282. Information on joint clinical assessments of the health technology in countries outside of EU is not relevant for the HTA process in Europe. **Suggestion for rewording:** "If HTA reports **of the medicinal product** from earlier joint assessments in the scope of the assessment **in accordance with Article 8(6) of regulation (EU) 2021/2282** ~~or from other jurisdictions~~ are available, these should be included."

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