EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 July 2025

Submission of comments on '

Concept paper on the revision of the guideline on the evaluation of anticancer medicinal products and appendices (EMA/122980/2025)

Comments from:

Name of organisation or individual
Institute for Quality and Efficicency in Health Care (IQWiG)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	IQWiG appreciates the opportunity to provide comments on the concept paper on the revision of the guideline on the evaluation of anticancer medicinal products and appendices.	
	In general, requirements for drug development should not only take the decisions by regulatory agencies into consideration. Due to the fact that immediately after regulatory approval also other decisions have to be taken, the needs of these decision makers should also be met by the drug development programme as much as possible. These decision makers include HTA bodies and payers, clinical guideline developers as well as patients and their physicians. Otherwise, downstream decisions may have to be postponed to collect additional information or decisions are highly uncertain. This may result in delays in access for patients to new drugs or in suboptimal use of new treatment within a treatment landscape. While ensuring that the needs of downstream decision makers are met is not primarily the responsibility of regulatory agencies, regulatory guidance documents are still shaping drug development programmes. The revision of the cancer guidance therefore is an opportunity to ensure that pre- and post-approval studies also support other decision makers.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
36-37		Comment: With regard to adjuvant, neoadjuvant and perioperative settings it will be important to define requirements that enable decision making for each of the components of these treatment strategies. Currently, from the studies conducted for regulatory approval it often is not possible to assess e.g. the benefit and harms of the neoadjuvant and adjuvant component of a perioperative treatment strategy separately. However, this is required to avoid overtreatment and enable efficient drug use limiting toxicities for patients as much as possible. Explicit guidance on studies in such settings and corresponding decision making are required for treatment optimisation. Issues with regard to current studies in these settings are e.g. described in the following publications: Navigating the complexity: reflections on the development of perioperative cancer treatments Zosso-Pavic, Matea et al. The Lancet Oncology, Volume 26, Issue 6, 675 - 678 https://pubmed.ncbi.nlm.nih.gov/40449493/ A conceptual framework for cautious escalation of anticancer treatment: How to optimize overall benefit and obviate the need for de-escalation trials Pourmir et al. Cancer Treatment Reviews 124 (2024) 102693	

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		https://www.cancertreatmentreviews.com/article/S0305-7372(24)00011-2/abstract	
38-39		Comment: A revision of condition specific guidance should include the definition of core outcomes sets per condition. Core outcomes sets are an important instrument for more efficient drug development. They also enable across-study analyses and thus learning beyond individual studies.	
45 - 54		Comment: The estimand framework is a valuable tool to clarify the interpretation of treatment effects and should be implemented in the revised guideline. We would like to emphasise the opportunity to address multiple estimands in a clinical trial, in order to meet the needs of regulators and Health Technology Assessment bodies (HTAb) simultaneously. This approach was discussed at the joint EMA/HTAb workshops in 2024 and 2025 and should be pointed out in the revised guidance (https://www.iqwig.de/printprodukte/joint-htab-regulatory-perspectives-on-understanding-evidence-challenges-final.pdf). Proposed change (if any): –	
55-65		Comment: DFS endpoints are used in treatment situations where patients are considered tumour-free. EFS endpoints are frequently used in neoadjuvant treatment settings and haematological malignancies. Addressing these treatment situations in more detail is necessary and therefore	

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		appreciated. It should be clarified in Appendix 1 that all events in DFS/EFS endpoints need to reflect the objective failure of curation in the investigated line of treatment. Therefore, events such as the start of a new anti-neoplastic therapy should not be accepted as qualifying events in DFS/EFS endpoints. Proposed change (if any): –	
55-57		Comment: Time-to-event analyses should not be limited to PFS/DFS or other benefit endpoints. The revision of the guidance should also describe more appropriate analyses of adverse events (which among other things may include time-to-event analyses). Specifically, in cancer trials which often have a different duration of observation in the treatment arms, an analysis of the frequency of adverse events (i.e. patients with events per arm) is highly biased. (see also: Unkel et al. On estimands and the analysis of adverse events in the presence of varying follow-up times within the benefit assessment of therapies. https://onlinelibrary.wiley.com/doi/epdf/10.1002/pst.1915) Appropriate analyses taking these study characteristics into consideration should be required. These analyses should also take the burden for patients due to the duration of adverse events into consideration (a CTCAE Grade 2 event with a long duration can be much more burdensome than a CTCAE Grade	

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		3 event with a short duration).	
66-72		Comment: From the reflection paper it seems that only appendices 1 and 4 will be updated. In addition, it will be important to also update Appendix 2 on patient-reported outcomes (PROs). Given the relevance of PROs specifically in cancer trials and treatment and the relevant developments in this field (e.g. by the SPIRIT-PRO or SISAQoL), a revision of the appendix is very important.	
68-83		Comment: Specifically addressing evolving areas in clinical development, such as treatments in earlier clinical settings (e.g., including neoadjuvant, adjuvant, perioperative), with curative versus palliative intent and treatments in haematological malignancies should also include revising Appendix 2 The use of patient-reported outcome (PRO) measures in oncology studies. Problems with PRO assessments regularly arise in situations where different treatment strategies are compared (e. g. single treatment vs. continuous treatment). PROs need to be collected during all relevant treatment phases in a balanced manner to allow fair comparison between treatment arms. Guidance on this matter is essential to generate meaningful data on PROs. Proposed change (if any):	

Please add more rows if needed.