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CHMP Oncology Working Party

Concept paper on the revision of the guideline on the evaluation of anticancer medicinal products and appendices

Agreed by ONCWP	19 March 2025
Adopted by CHMP for release for consultation	14 April 2025
Start of public consultation	30 April 2025
End of consultation (deadline for comments)	31 July 2025

The proposed guideline will replace 'Guideline on the clinical evaluation of anticancer medicinal products' (EMA/CHMP/205/95 Rev.6); Appendix 1 "Methodological Considerations on using PFS / DFS as a primary endpoint in Oncology" (EMA/CHMP/27994/2008/Rev.1); Appendix 4 "Condition Specific Guidance" (EMA/CHMP/703715/2012/Rev.2)

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1. Introduction

Clinical developments and marketing authorisation applications of anticancer medicines for patients with solid tumours and haematological malignancies have been markedly increasing over recent years. To provide timely guidance on scientific and regulatory aspects, several revisions of the "Guideline on the clinical evaluation of anticancer medicinal products" (currently applicable Rev.6) have been issued. This main guideline document is complemented by a number of appendices that address more specific areas.

This concept paper introduces revision 7 of the "Guideline on the evaluation of anticancer medicinal products", which proposes amendments and restructuring to the current version of the document. It also proposes to amend and restructure the appendices for a more user-friendly presentation. Furthermore, it incorporates feedback received during consultation of the previous version revision.

2. Problem statement

The initiation of Revision 7 is driven by the need to align the guideline with evolving regulatory and scientific developments and to implement the estimands framework introduced by ICH E9(R1) addendum[1]. The value of the estimands framework is recognised, as reflected in recent discussions within CHMP, including scientific advice procedures, the recently revamped CHMP assessment report templates[2], the CHMP-endorsed Methodology Working Party workplan[3] and scientific literature.

Furthermore, Revision 7 will introduce other updates, including the addition of sections dedicated to haematological cancers where appropriate, improvements to the guidance on single-arm trials following the publication of the single-arm trials (SAT) reflection paper[4], and a revision of the guidance on regulatory standards for clinical trials in adjuvant, neoadjuvant and perioperative settings. The revision will also entail a comprehensive review of Appendix 4 on condition-specific guidance, including whether the guidance structure should be maintained or updated as standalone documents.

Furthermore, structural changes will be made to avoid overlapping information under different headings, with annexes and appendices streamlined into a more user-friendly structure and updated as needed. Where appropriate, the use of AI-driven language models may be explored as a methodological tool to support text modifications to enhance clarity throughout the document.

3. Discussion (on the problem statement)

The implementation of the ICH E9 (R1) addendum is a key priority for this revision. The estimands framework applies across the entire clinical trial process, from planning and design to conduct, data collection, analysis and interpretation of results.

The specific updates to implement estimands framework in oncology trials will focus on:

- Clearly defining the question of interest, including the handling of relevant intercurrent events
- Regulatory expectations for the primary estimand in pivotal trials
- Clearly distinguishing between the defined estimand of interest and the selection of adequate statistical methodology for estimating the effect (including e.g., censoring rules)

[1] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-and-sensitivity-analysis-clinical-trials-guideline-statistical-principles-clinical-trials-step-5_en.pdf
[2] https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/assessment-templates-guidance
[3] https://www.ema.europa.eu/en/documents/other/consolidated-3-year-rolling-work-plan-methodology-working-party-2025-2027_en.pdf
[4] Establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation | European Medicines Agency (EMA) (europa.eu)

- Clarifying the role of supplementary and sensitivity analyses, and providing guidance on appropriate sensitivity analyses for the primary estimand (e.g. tipping point analysis)

As the first step, the relevant questions of interest in the context of time-to-event endpoints, as discussed in the Appendix 1 (PFS/DFS) and other endpoints reflected in the main guideline, will be revisited. Additionally, the estimands framework will be applied to single-arm trials. Since the scientific and clinical research questions of interest vary by disease, condition and clinical setting (e.g. early versus late-stage, curative versus palliative intent), the revision of the main guideline and certain condition-specific appendices will progressively implement the estimands framework.

Furthermore, evolving areas in clinical development, such as treatments in earlier clinical settings (e.g., including neoadjuvant, adjuvant, perioperative), with curative versus palliative intent, and related guidance will be addressed. Finally, the review of topics published under Condition-Specific guidance (Appendix 4) and the addition of new topics (e.g. for haematological malignancies) will be prioritised.

Therefore, based on the issues described above, the following sections of the guideline and relevant appendices will be updated:

- Appendix 1: "Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials"[5]
- Appendix 4: "Condition Specific Guidance"[6] will be reviewed, including the possibility of replacing this guidance with individual reflection papers, which can be revised independently, as necessary
- Guideline on the clinical evaluation of anticancer medicinal products" (current Rev.6)
    - Reconsideration within the ICH E9(R1) addendum with updates of specific sections (e.g. section 2)
    - Amendments in the section on single-arm trials following the publication of the SAT reflection paper (EMA/CHMP/430688) which will improve guidance, clarify recommendations and avoid inconsistencies
    - Addition of guidance dedicated to haematological cancers where appropriate
    - Other potential changes include the update of sections on regulatory standards for clinical trials in adjuvant, neoadjuvant and perioperative settings
- The main guideline and relevant appendices will also be restructured to improve readability and to enable readers to more effective navigate through the information.

4. Recommendation

The Oncology Working Party (ONCWP) at the EMA recommends the drafting of the Revision 7 of the Guideline for the development of anticancer medicinal products and relevant appendices taking into account the issues identified above.

[5] https://www.ema.europa.eu/en/documents/scientific-guideline/appendix-1-guideline-evaluation-anticancer-medicinal-products-man-methodological-consideration-using-progression-free-survival-or-disease-free-survival-confirmatory-trials_en.pdf
[6] https://www.ema.europa.eu/en/documents/scientific-guideline/evaluation-anticancer-medicinal-products-man-appendix-4-condition-specific-guidance-revision-2_en.pdf

5. Proposed timetable

This concept paper is to be released for a 3-month public consultation. The draft revision 7 of the main guideline document and relevant appendices will then be developed and released within 12 months after adoption of the concept paper by the CHMP. This draft will then be subject to a 6-month public consultation. The revised guideline is expected to be finalised within approximately 12 months of the end of the public consultation.

6. Resource requirements for preparation

This revision will involve the ONCWP, and experts from the methodology working party (MWP) and the Oncology European specialised expert communities (ESEC) appointed as part of the temporary Drafting Group. The Scientific Advice Working Party (SAWP) and MWP will be consulted during the development of the draft guidance.

7. Impact assessment (anticipated)

It is anticipated that the proposed guideline revision will have a major impact on drug development. By providing guidance on the estimands framework implementation, it will drive the clinical trials planning and design as well as their conduct, data collection and analysis. Consequently, this will improve the assessment of relevant treatment effects and the interpretation of study results moving forward, which in turn will improve decision-making by regulators, potentially health technology assessment (HTA) bodies, as well as further inform physicians and patients.

It is also expected that this revision will have an impact on the content of CHMP scientific advice and regulatory submissions for oncology medicinal products.

Furthermore, adequate structural revisions will enable better access and usability of the guideline.

8. Interested parties

Healthcare professionals, pharmaceutical industry, patient organisations, relevant European learned societies involved in research in oncology and relevant academic and non-profit cancer organisations.