



1 19 March 2025  
2 EMA/122980/2025  
3 CHMP Oncology Working Party

4 **Concept paper on the revision of the guideline on the**  
5 **evaluation of anticancer medicinal products and**  
6 **appendices**  
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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

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

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14 Comments should be provided using this EU Survey [form](#). For any technical issues, please contact  
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Keywords	Cancer, estimands
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## 17 **1. Introduction**

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

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

## 28 **2. Problem statement**

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

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

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

## 44 **3. Discussion (on the problem statement)**

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

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

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

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<sup>1</sup> [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](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)

<sup>2</sup> <https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/assessment-templates-guidance>  
<sup>3</sup> [https://www.ema.europa.eu/en/documents/other/consolidated-3-year-rolling-work-plan-methodology-working-party-2025-2027\\_en.pdf](https://www.ema.europa.eu/en/documents/other/consolidated-3-year-rolling-work-plan-methodology-working-party-2025-2027_en.pdf)

<sup>4</sup> [Establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation | European Medicines Agency \(EMA\) \(europa.eu\)](https://www.ema.europa.eu/en/documents/scientific-guideline/establishing-efficacy-based-on-single-arm-trials-submitted-as-pivotal-evidence-in-a-marketing-authorisation_en.pdf)

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

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

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

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

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

## 84 **4. Recommendation**

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

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<sup>5</sup> [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](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)

<sup>6</sup> [https://www.ema.europa.eu/en/documents/scientific-guideline/evaluation-anticancer-medicinal-products-man-appendix-4-condition-specific-guidance-revision-2\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/evaluation-anticancer-medicinal-products-man-appendix-4-condition-specific-guidance-revision-2_en.pdf)

## 88 **5. Proposed timetable**

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

## 94 **6. Resource requirements for preparation**

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

## 99 **7. Impact assessment (anticipated)**

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

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

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

## 109 **8. Interested parties**

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