EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Concept Paper for the Development of a Guideline on Non-Inferiority and Equivalence Comparisons in Clinical Trials

Agreed by Methodology Working Party	20 October 2023
Adopted by CHMP for release for consultation	February 2023
Start of public consultation	16 February 2023
End of consultation (deadline for comments)	31 May 2024

The proposed guideline will replace CPMP/EWP/482/99: "Points to consider on Switching between Superiority and Non-Inferiority" and CPMP/EWP/2158/99 "Guideline on the Choice of Non-Inferiority Margin".

Comments should be provided using this EU Survey form. For any technical issues, please contact the EUSurvey Support.

Keywords	Non-inferiority comparisons, randomised controlled trials, non-inferiority margins, active comparators, estimands

1. Introduction

Non-inferiority comparisons to active comparators are frequently used in drug development and specifically, in phase 3 trials, intended to provide pivotal evidence for marketing authorisation applications. Specific issues related to non-inferiority and therapeutic equivalence comparisons require considerations different from those encountered in superiority trials. Two EMA guidance documents on this issue are currently available, the Guideline on the Choice of Non-Inferiority Margin, adopted by the CHMP in 2005, and the Points to consider on Switching between Superiority and Non-Inferiority, adopted by the CHMP in 2000. Following methodological developments, as outlined in the subsequent sections, it is suggested merging and consolidating both documents in a new guideline to include these developments.

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2. Problem statement

The development of the estimand framework as outlined in the ICH E9 (R1) Addendum on Estimand and Sensitivity Analysis in Clinical Trials revealed the necessity of specific recommendations about the application of the estimand framework to the non-inferiority and therapeutic equivalence settings. Non-inferiority trials are intended to show that the efficacy of a new medicinal product is not considerably inferior to an active comparator. As an equivalence statistical test consists of two non-inferiority tests, many considerations relevant to non-inferiority trials are also applicable to demonstrate therapeutic equivalence.

Generally, the sensitivity of a trial to detect differences between treatments is paramount to avoid a false decision on non-inferiority or equivalence comparisons. Lack of sensitivity may be related to the study design and conduct, including the choice of estimand. Therefore, it is important to target an estimand adapted to the specific setting of a non-inferiority or equivalence comparison. Current EMA guidance requires similar conclusions from statistical analyses in two different analysis sets, the full analysis set and the per-protocol analysis set. However, the ICH E9 (R1) Addendum recognises issues related to the per-protocol analysis set, specifically the deviation from the Intention-to-treat (ITT) principle and that it may not be possible to construct a relevant estimand to which a statistical analysis based on the per-protocol analysis set can be aligned. It is acknowledged that motivation for using a per-protocol analysis is to be more sensitive to detect differences between treatments by avoiding diluting effects caused by protocol deviations. Consequently, special considerations for applying the estimand framework are required, constructing an estimand that targets a treatment effect that prioritises sensitivity to detect differences, along with statistical analyses that are unbiased or conservative with respect to the corresponding estimand and the null hypothesis of a non-inferiority comparison.

In addition to new considerations on the estimand framework, the justification and derivation of the non-inferiority margin played a key role in sponsor-regulator Scientific Advice interactions since the publication of the EMA non-inferiority guidelines which highlighted the need to consider the following trial objectives separately. There are different objectives in a non-inferiority or therapeutic equivalence trial: (1) the putative placebo comparison to demonstrate efficacy of the new treatment, (2) the assessment of the benefit relative to the comparator (e.g. for additional claims), (3) the intention to demonstrate that the new treatment is not harmful (non-inferior safety vs. placebo) and (4) therapeutic equivalence for biosimilars. Hence, the margin needs to be justified in line with the objective requiring a more detailed discussion.

Finally, it is recognised that the generation of a single guideline on non-inferiority and therapeutic equivalence comparisons would facilitate the compilation of the related regulatory requirements.

3. Discussion (on the problem statement)

The following topics will be addressed:

- The different types and objectives of non-inferiority and equivalence trials;
- Trial quality and assay sensitivity;
- Estimands, including specific issues relevant to non-inferiority and equivalence comparisons;
- Justification of the non-inferiority margin for the different objectives including difficulties to define the margin;

- Statistical analysis, including analysis sets, treatment of missing data related to the estimand(s), and sensitivity analysis;
- Multiplicity issues;
- Switching between non-inferiority and superiority comparisons;
- Trials including non-inferiority and superiority comparisons in the statistical testing procedure.

4. Recommendation

The Methodology Working Party recommends drafting a guideline on non-inferiority and therapeutic equivalence comparisons taking into account the issues identified above.

5. Proposed timetable

Establishment of drafting group 02/2024, discussion at CHMP 09/2024, proposed date for release of draft guideline 10/2024, deadline for comments 01/2025, discussion at the Methodology Working Party (MWP) 03/2025. Expected date for adoption by CHMP 09/2025.

6. Resource requirements for preparation

The core drafting group will be a writing team of six people including clinical experts. A wider group of six additional contributors is foreseen for discussion and review. The core drafting group will attend twice monthly meetings; the wider drafting group will convene monthly.

A wider meeting is anticipated during guideline development with the Methodology Working Party, its European Specialised Expert Community (ESEC) and designated stakeholders. A workshop with external stakeholders at the end of the draft guideline writing process is considered.

7. Impact assessment (anticipated)

It is anticipated that this document will provide clarity and advice with respect to the application of the estimand framework for non-inferiority comparisons, the justification of the non-inferiority margin as well as the design of therapeutic equivalence trials. It will improve planning of confirmatory trials that include non-inferiority comparisons and therapeutic equivalence comparisons by sponsors and lead to improved scientific advice and regulatory assessment.

8. Interested parties

CHMP and its working parties, especially the Scientific Advice Working Party (SAWP), are the two main regulatory stakeholders that will be highly affected by this Guideline. Other regulatory stakeholders, which will likely be affected differently, are the Committee for Advanced Therapies (CAT), the Paediatric Committee (PDCO), the Pharmacovigilance Risk Assessment Committee (PRAC) and the Committee for Orphan Medicinal Products (COMP). All of the aforementioned stakeholders will be consulted prior to releasing the draft to the public.

The Guideline will also benefit from the input of other regulatory agencies (e.g. FDA, PMDA).

Developers of new medicines from industry and academia as well as researchers conducting clinical trials will be provided guidance and clarity on the related issues and will be affected by the pertinent regulatory requirements.

9. References to literature, guidelines, etc.

CPMP/ICH/363/96: ICH E9 "Statistical Principles for Clinical Trials"

CPMP/ICH/364/96: ICH E10 "Choice of Control Group in Clinical Trials"

CPMP/EWP/908/99: "Points to consider on Multiplicity Issues in Clinical Trials"

CPMP/EWP/2158/99 "Guideline on the Choice of Non-Inferiority Margin"

CPMP/EWP/482/99 "Points to consider on Switching between Superiority and Non-Inferiority"

CHMP/ICH/436221/2017 ICH E9 (R1) Addendum on "Estimands and Sensitivity Analysis in Clinical Trials"