



ICH E9(R1) Estimands and Sensitivity Analysis in Clinical Trials

Training Module 1: Summary

Addendum to ICH E9 – Statistical Principles for Clinical Trials

ICH E9(R1) Expert Working Group
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Introduction note

These slides were produced as training material to accompany the ICH E9(R1) addendum.

The intention is to support the scientific community in the comprehension of a new framework to define estimands based on the trial objective and considering intercurrent events. For this purpose, most of the content of this addendum is presented in a practical fashion, accompanied by examples dealing with estimands and sensitivity analysis in clinical trials, based on the experience of Expert Working Group members.

The training material is divided in three main modules: module 1 (summary), module 2 (comprehensive slide deck) and module 3 (generic example). Module 2 is composed by 6 submodules that correspond to sections A.1 to A.6 of the addendum.

Training modules

- **Module 1: Summary**
- Module 2: Comprehensive slide deck
 - Module 2.1: Introduction
 - Module 2.2: Framework
 - Module 2.3: Estimands
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 - Module 2.5: Impact on trial analysis
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- Module 3: Generic example

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Summary

The addendum aims to improve the planning, design, analysis and interpretation of clinical trials.

- Clear trial objectives should be translated into key clinical questions of interest by defining suitable **estimands**.
- An **estimand** (i.e. “what is to be estimated”) is a precise description of the treatment effect reflecting the clinical question posed by the trial objective.
 - It summarises at a population level what the outcomes would be in the same patients under different treatment conditions being compared.

Summary

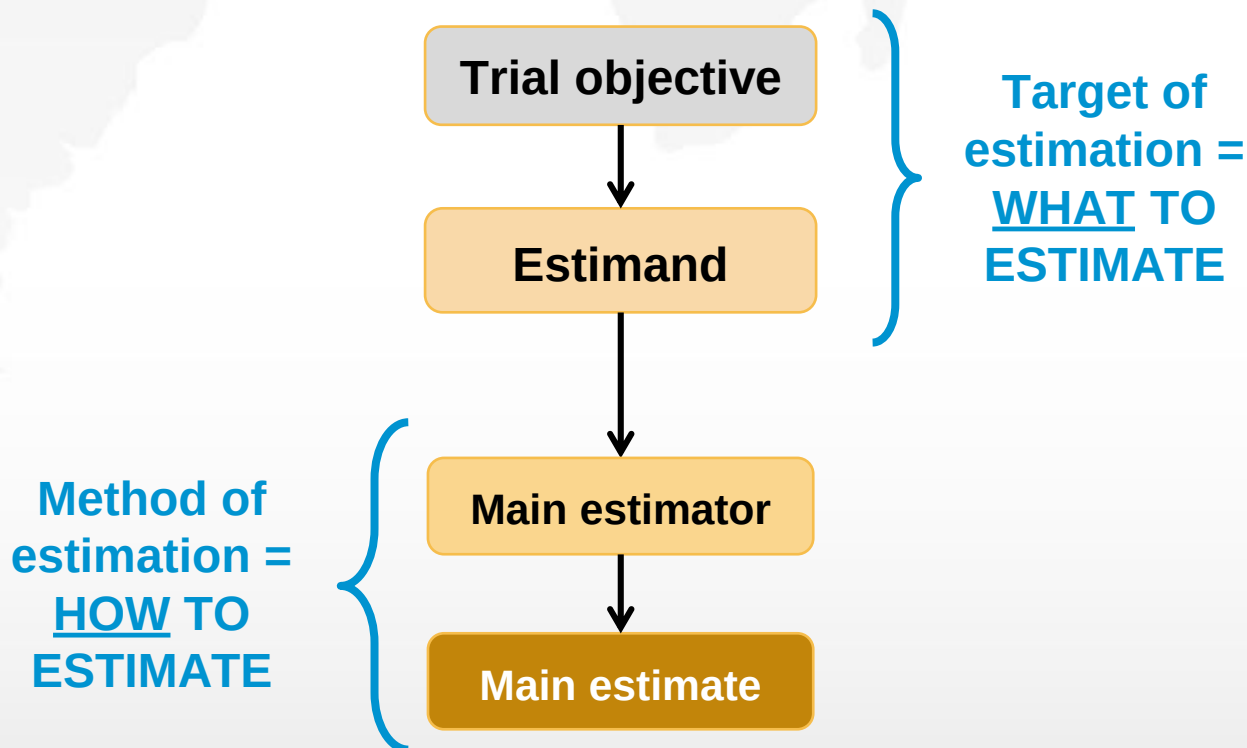
The addendum aims to improve the planning, design, analysis and interpretation of clinical trials.

- **Without** a precise description of the trial objective and the treatment effect that is targeted for testing and estimation there is a risk that:
 - the study **will not be designed appropriately** to address its objective;
 - the statistical analyses will be **misaligned** to the trial objective and the target of estimation;
 - the treatment effect that is reported will be **incorrectly interpreted**, which risks **misleading** decision makers.

This is important for all researchers and healthcare professionals designing, conducting, or interpreting a clinical trial

Summary

This addendum presents a structured framework to link trial objectives to a suitable trial design and tools for estimation and hypothesis testing.



Summary

- Having clarity in the trial objectives when describing the treatment effect of interest at the planning stage should **inform appropriate choices** about trial design, data collection and statistical analysis.
- The addendum aims to facilitate dialogue regarding the treatment effects that a clinical trial seek to estimate:
 - **between disciplines** (clinician, statistician, etc);
 - **between sponsor and regulator**.

Summary

- The description of an estimand will not be complete without reflecting how potential **intercurrent events** are addressed in the clinical question of interest.
- **Intercurrent events** are events occurring after treatment initiation and affect either the interpretation or the existence of the measurements associated with the clinical question of interest, e.g.:
 - use of an alternative treatment, perhaps a rescue medication;
 - discontinuation of treatment;
 - terminal events such as death.
- Missing values due to e.g. study withdrawal or loss-to-follow-up are **not intercurrent events** and are not to be reflected in the estimand, but instead represent limitations to the data that need to be addressed in the statistical analysis.

Summary

- Different **strategies** are introduced to address potential **intercurrent events** reflecting the clinical question of interest.
- The **choice of strategy** for each intercurrent event should be the subject of **multi-disciplinary discussion** between, e.g. clinicians and statisticians, and discussion between sponsor and regulator.
- Disease under study, clinical context (e.g. availability of other treatments), administration of treatment, and goal of treatment will influence the choice of strategies. The experimental situation should also be considered as it may differ to that which is anticipated in clinical practice.
- **Different strategies** will often be used to reflect the clinical question of interest in respect of **different intercurrent events**.

Summary

- Having specified an **estimand** (= WHAT TO ESTIMATE), the addendum addresses **impact on trial design, conduct and analysis** (= HOW TO ESTIMATE).
- In respect of estimation, the addendum calls for greater precision on what is labelled as '**missing data**'. Specifically, having clarity in the estimand and the methods for estimation gives a basis for planning **which data need to be collected** and hence which data, when not collected, present a missing data problem to be addressed.

Summary

- The addendum gives a more precise focus to requirements for **sensitivity analysis**.
- With an agreed estimand, and a pre-specified statistical analysis that is aligned to that estimand, sensitivity analysis can focus on **sensitivity to deviations from assumptions** in respect of a particular analysis, rather than sensitivity to the choice of analytic approach.
- **Supplementary analysis** for an estimand can also be planned in order to more fully investigate the trial data and understand the treatment effect, **complementing** the main and sensitivity analyses.

Summary

- The addendum calls for changes in **trial documentation**.
- Estimands should be defined and **explicitly specified in the clinical trial protocol**.
- The protocol and the statistical analysis plan should pre-specify the **main estimator for each estimand**, together with a suitable **sensitivity analysis** to explore the robustness under deviations from its assumptions.
- While the primary estimand will be the main drive for the study design, estimands for **secondary trial objectives** that are likely to support regulatory decisions should also be defined and specified explicitly.

Next module:

2.1. Introduction

Understanding treatment effects and motivation for the ICH E9(R1) addendum. Scope of the document and examples.