



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

Training Module 2.5: Impact on trial analysis

Addendum to ICH E9 – Statistical Principles for Clinical Trials

ICH E9(R1) Expert Working Group
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Disclaimer

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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
 - Module 2.4: Impact on trial design and conduct
 - **Module 2.5: Impact on trial analysis**
 - Module 2.6: Documenting estimands and sensitivity analysis
- Module 3: Generic example

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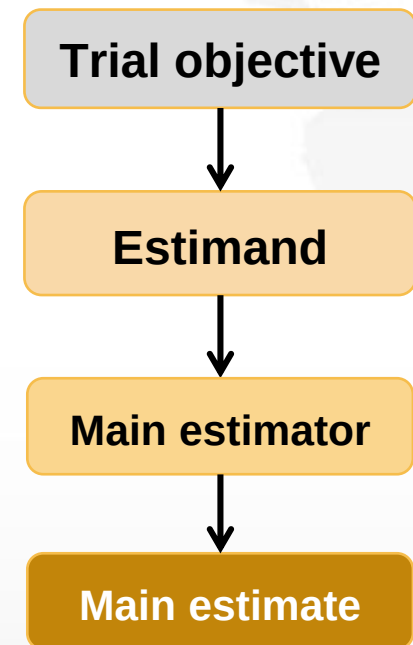
- **A.1. Purpose and Scope** **Module 2.1**
- **A.2. A Framework to Align Planning, Design, Conduct, Analysis and Interpretation** **Module 2.2**
- **A.3. Estimands**
 - A.3.1. Intercurrent Events to be Reflected in the Clinical Question of Interest
 - A.3.2. Strategies for Addressing Intercurrent Events when Defining the Clinical Question of Interest
 - A.3.3. Estimand Attributes
 - A.3.4. Considerations for Constructing an Estimand**Module 2.3**
- **A.4. Impact on Trial Design and Conduct** **Module 2.4**
- **A.5. Impact on Trial Analysis**
 - A.5.1. Main Estimation
 - A.5.2. Sensitivity Analysis
 - A.5.2.1. Role of Sensitivity Analysis
 - A.5.2.2. Choice of Sensitivity Analysis
 - A.5.3. Supplementary Analysis**Module 2.5**
- **A.6. Documenting Estimands and Sensitivity Analysis** **Module 2.6**
- **Glossary**

Outline of Module 2.5

- Main estimation
- Sensitivity analysis
- Role of sensitivity analysis
- Choice of sensitivity analysis
- Supplementary analysis

Main estimation

- An analytic approach, or **estimator**, that is **aligned with a given estimand** should be implemented .
- For example, if addressing use of rescue medication with a **treatment-policy strategy**:
 - ✓ Analysis based on **continued data collection after the intercurrent event** and use of those observed data in the analysis would be **‘aligned’** to the estimand, 👍
 - ✗ Not attempting to collect those data and/or regarding data after rescue medication as ‘missing’ then **analysing through MMRM with a MAR assumption** would **not be aligned** to the estimand. 👎

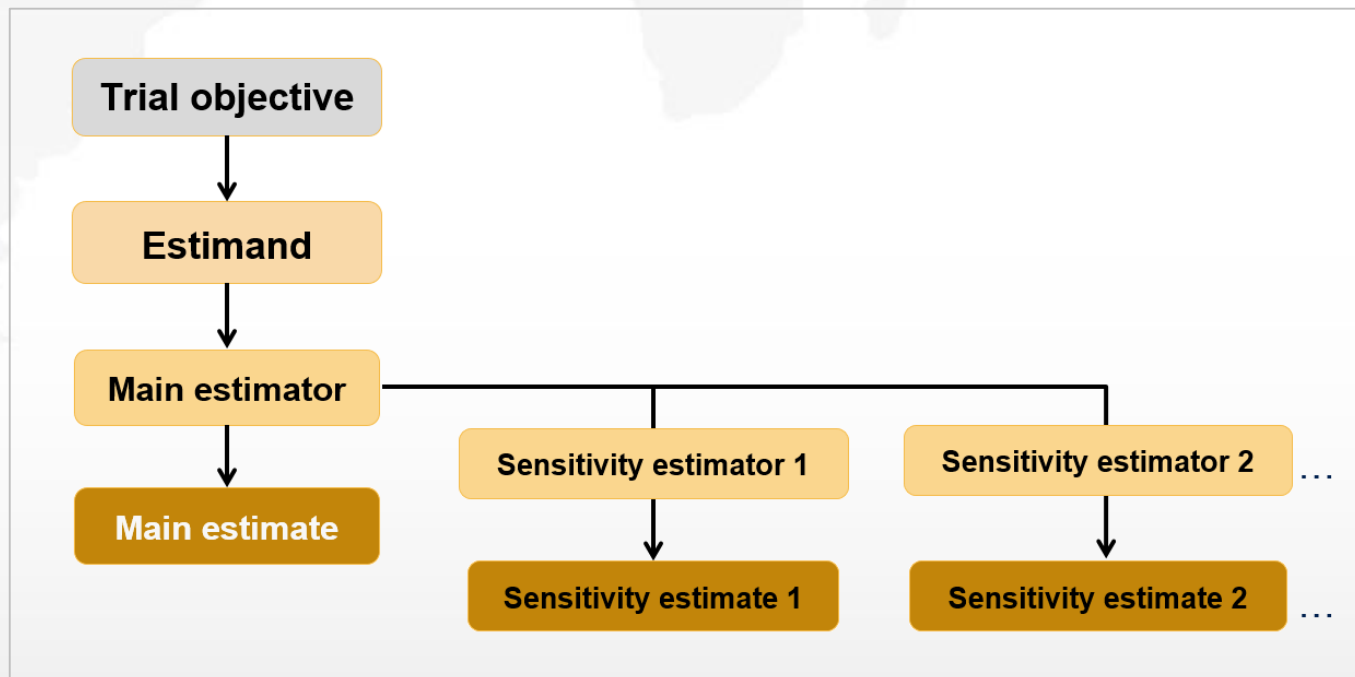


Main estimation

- The **estimator** selected should be able to provide an **estimate** on which a **reliable interpretation can be based**.
- An important consideration for whether a reliable estimate will be available is the **number and plausibility of assumptions that need to be made** in the main analysis, including those associated with the use of modelling, prediction or imputation to address missing data.

Main estimation

- Any **assumptions made should be explicitly stated**, and **sensitivity analysis** should be used to assess the robustness of the results to the underlying assumptions, aligned to one estimand.



Sensitivity analysis

Sensitivity analysis Is a series of analyses conducted with the intent to explore the robustness of inferences from the main estimator to deviations from its underlying modelling assumptions and limitations in the data.

Sensitivity analysis definition, ICH E9(R1) addendum

Main estimation: missing data

- The addendum calls for **greater precision on what is labelled as ‘missing data’**.
- Assessments scheduled **after an intercurrent event has occurred** (e.g. discontinuation of treatment) **should not** automatically **be set to missing**. If the treatment policy strategy is selected, in particular, maximising the collection of post-intercurrent event data would limit the reliance on the assumptions on mechanisms for missingness.
- Having clarity in the estimand 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.

Missing data

Missing data Data that would be meaningful for the analysis of a given estimand but were not collected. They should be distinguished from data that do not exist or data that are not considered meaningful because of an intercurrent event.

Missing data definition, ICH E9(R1) addendum

Main estimation: missing data

- For example:
 - If planning to address the use of rescue medication with the **treatment-policy strategy**, assessments scheduled after the use of rescue medication should continue as planned. Any assessments not taken are '**missing data**'.
 - If planning to address the use of rescue medication with **a hypothetical strategy**, the relevance of the assessments scheduled after the use of rescue medication for estimation depends on the estimator(s) chosen.
- **Methods to address** the problem presented by **missing data** can be selected to **align with the chosen estimand**.

Role of sensitivity analysis

- Sensitivity analysis is used to evaluate the **robustness of inferences** made on a particular estimand to **limitations in the data** and **deviations from the assumptions** used in the statistical model for the main estimator.
- 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.

Role of sensitivity analysis

- In general, the **statistical assumptions** that underpin the main estimator should be **clearly documented**.
- **A sensitivity analysis**, focused on the same estimand, should then be **pre-specified** to investigate the impact of deviations from these assumptions. This might be characterised as the extent of departures from assumptions that change the interpretation of the results in terms of their statistical or clinical significance (e.g., tipping point analysis).
- Whilst the While on Treatment and the Composite strategies do not make estimating assumptions (but have to be justified in terms of **interpretability**), and in the Treatment Policy strategy the impact of assumptions can be reduced by maximising **data collection**, the Hypothetical and Principal Stratum strategies necessarily imply strong **assumptions**.

Supplementary analysis

- Supplementary analysis should be clearly **distinguished from sensitivity analysis**, and in general, should be given a **lower priority** relative to a sensitivity analysis.
- **Any other analysis** that is planned, presented or requested in order to more fully investigate and understand the trial data and the effects of treatment is referred to as a **supplementary analysis**.

Supplementary analysis

Supplementary analysis Is a general description for analyses that are conducted in addition to the main and sensitivity analysis to provide additional insights into the understanding of the treatment effect. The term describes a broader class of analyses than sensitivity analyses.

Supplementary analysis definition, ICH E9(R1) addendum

Next module:

2.6. Documenting estimands and sensitivity analysis

**Impact of the addendum on protocol
writing, study design, data analysis and
interpretation**