



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

Training Module 2.4: Impact on trial design and conduct

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
 - **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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Outline of Module 2.4

- ICH E9(R1) will have implications on how we design and conduct clinical trials and perform statistical analyses
- Identification of estimand(s) at the design stage requires informed discussion with all stakeholders
- Certain estimands may require or benefit from non-standard designs and/or endpoints

Impact on Trial Design

- The **design of a trial** needs to be **aligned to the estimands** that reflect the **trial objectives**.
- **ICH E6** lists important aspects of **trial design** that should be stated in the **protocol**. **Alignment with the trial objective and estimand** should be sought when considering, for example:
 - The type of trial (e.g., double-blind, placebo-controlled, parallel design);
 - Duration of subject participation, discontinuation criteria for individual subjects, subject withdrawal criteria, medications permitted before and during the trial;
 - Methods for timing and assessing variables, procedures for monitoring subject compliance, specification of efficacy and/or safety parameters;
 - The methods and timing for assessing, recording, and analysing efficacy and/or safety parameters.

Impact on Data Collection

- The estimators chosen for the agreed **estimand dictate the data that need to be collected** during the trial.
- **Different estimands** (even within those targeted in one trial) might have **different requirements** regarding data collection.
- A trial design that is suitable for one estimand **might not be suitable** for other estimands of potential importance.



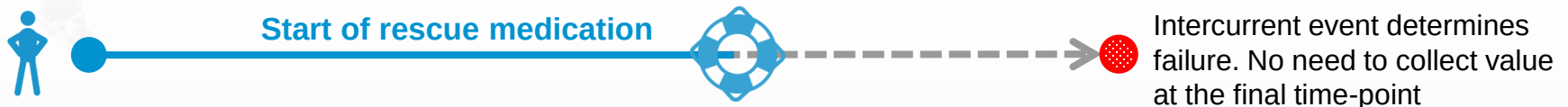
The **amount of patient withdrawals** from the study does **not influence** the relevance of a particular strategy or estimand, but the **impact** of potential patient withdrawals on estimation needs careful consideration.

Impact on Data Collection

- An estimand based on a **treatment policy strategy** requires the value for the variable to be **collected for all subjects regardless** (i.e. before and after) **of the intercurrent event**.



- In contrast, an estimand in which the variable is defined as a composite of no use of rescue medication and a favourable clinical outcome **does not require collection of data after the use of rescue medication**.



Efforts should be made to **collect all data that are relevant to support a statistical analysis aligned to the estimands of interest**, including data for the **characterisation, occurrence and timing of intercurrent events**.

Impact on data collection

- Missing data is inevitable in certain scenarios (e.g. administrative censoring, loss to follow-up); these potential scenarios should be well justified.
- However, in situations of treatment discontinuation, use of rescue medication, etc. **data can still be collected**. These data may not be relevant anymore, depending on the chosen strategy and estimator.
- For terminal events (e.g. death), data cannot be collected, but this is also **not missing data**.
- Data that are necessary to estimate the estimand but not collected will lead to a **missing data problem** that has to be **addressed through statistical inference** (with consequent issues regarding untestable assumptions and robustness of results).

Impact on data collection

- A **prospective plan to collect reasons** why data intended for collection are missing is helpful for distinguishing between intercurrent events and missing data.
 - Modify eCRFs to prompt collection of the reason for study withdrawal with **more granularity**, e.g. discontinuation due to patient's decision is not detailed enough.
 - A statement like “loss to follow-up” does not directly inform on treatment discontinuation, which should be **recorded separately**.
 - There should also be an indication if treatment discontinuation happened **due to lack of efficacy or toxicity**.
- Some measures can be implemented in the trial to reduce or avoid intercurrent events that would normally occur in clinical practice. It is important to ensure that they do not affect the **external validity** of the trial.

Design Options

- **Randomisation** and **blinding** remain cornerstones of controlled clinical trials. Several **non-standard designs** are available that can be aligned to the choice of the estimand or estimands that reflect the primary trial objectives:
 - **Enrichment designs:** incorporate a run-in period in which a subset of the subjects are selected based on their likelihood of experiencing the intercurrent event of interest, e.g., the population of interest could be patients who tolerate the experimental treatment.
 - **Randomised withdrawal designs:** all subjects are initially treated with the experimental treatment, then, subjects that have a positive response to the experimental treatment are randomly selected either to remain on the experimental treatment or to be switched to placebo or alternative control.
 - **Titration designs:** permit flexible dosing to accommodate individual differences in drug response which may allow more subjects to continue on the assigned treatment by reducing number of intercurrent events.



Not all types of design may be acceptable in all situations. Appropriate **dialogue** with regulators may be necessary.

Other important aspects

- A **precise description of the estimand(s)** of interest should inform **sample size calculations**.
- For **synthesising evidence across clinical trials**, the same estimand should be considered at the planning stage of the contributing trials.
 - Similar considerations apply, for example, to the design of a **meta-analysis, using estimated effect sizes from completed trials to determine non-inferiority margins**, or the use of external control groups for the **interpretation of single-arm trials**.
- A trial may have **multiple objectives translated into multiple estimands**.
 - Multiplicity adjustment for multiple endpoints or multiple sub-groups can equally be applied to multiple estimands.

Next module:

2.5. Impact on trial analysis

Role and choice of sensitivity analysis and supplementary analysis in light of the estimand framework