Estimands in early phase studies

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Abstract

- An estimand is a precise description of a treatment effect associated with the objective(s) of a clinical trial.
- The ICH E9 R1 addendum presents guidelines on using the estimand framework, focused on confirmatory clinical trials, but these ideas are essential for all types of trials.
- Here, we present several examples based on real case studies that describe how the estimand framework can be helpful in early phase studies.
- We also describe how the estimand framework is important in discussions within early phase clinical project teams and should not be considered the sole concern of statisticians.

Introduction

- Before the ICH E9 R1 addendum, regulatory authorities were receiving analyses of very similar clinical trials from different sponsors that did not share the same interpretation of what constituted an Intention-To-Treat (ITT) or per protocol (PP) analysis.
- Although the ICH E9 R1 document was written due to problems with confirmatory trials, the principles and the framework were equally important for all types of trials. While the value they bring is more evident for Phase IIb trials, there is also some value in using the estimand framework for Phase IIa and earlier phase studies.
- The estimand framework offers a common "language" to understand and communicate clinical trial design, analyses, and results.

Estimand framework in a clinical trial

- The clinical objective, the reason for conducting the trial, aims to answer a specific scientific question and usually consists of several primary and secondary objectives.
- One way of precisely defining the estimand is to re-express the clinical objective through four attributes, together with an understanding of intercurrent events (ICEs).

The four estimand attributes are:

- **Treatment**
- Population
- *Variable of interest*
- Choice of summary measure

- *Intercurrent events* (ICEs) are events that may happen to study participants after initiation of treatment.
  - In practice, different events can occur for the study participants that are unplanned in the sense that they do not belong to the planned schedule of assessments for the study.

Examples of participant journeys in a study, showing occurrences of different types of intercurrent events:

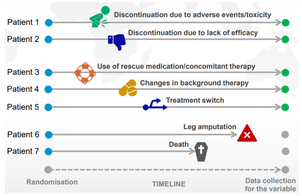
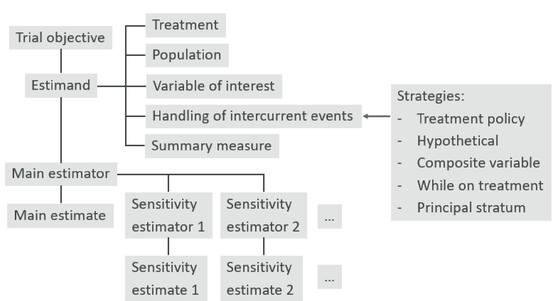


Figure adapted from "ICH E9(R1) Estimands and Sensitivity Analysis in Clinical Trials" presentation https://database.ich.org/sites/default/files/E9%28R1%29%20Training%20Material%20-%20PDF_0.pdf

Example in asthma illustrating the different estimand attributes and handling of ICEs:

Objective	Estimand description
Primary Objective: In patients with uncontrolled asthma treated with high dose ICS and LABA, what is the between group difference *in lung function, as measured by mean change from baseline in* FEV_1, **comparing treatment with investigational drug to placebo** at four weeks after randomisation, *regardless of treatment discontinuation*	*Endpoint: Change from baseline in FEV1 four weeks after randomisation* Population: *Patients with uncontrolled asthma treated with high dose ICS and LABA* *Intercurrent Events: Treatment policy. Actual values of the outcome are used, whether or not treatment has been discontinued.* Summary Measure: *Difference in means* **Treatment:** *Investigational drug or matched placebo*

Overview of the complete estimand framework, including the attributes of the estimand, handling of ICEs, and the estimator/estimate concepts. Note that every objective will have its own estimand:



Example 1: Should there be participant follow-up for efficacy endpoints after treatment discontinuation?

- In a Phase II study, participants are planned to come to the site for 4 post-randomization visits for specific efficacy-related measurements.
- **For participants who, due to safety signals, need to discontinue treatment after the second visit, do we still ask them to come to Visit 3 and 4 to assess their efficacy measurements?** Follow-up visits for safety will be conducted regardless.
- The answer depends on the scientific question of interest and the exact estimand that is associated with that question of interest:
  - For a treatment policy approach for this ICE, we will still need to follow participants for efficacy.
  - For hypothetical or while-on-treatment strategies, we would only use the data generated up until a participant discontinues treatment, and if either of those strategies were chosen, we do not need to keep following the participants for efficacy after treatment discontinuation.

Example 2: Interpretation of results given a large proportion of treatment discontinuation for placebo arm

- A Phase IIb study included 5 dose arms of the new drug compound under investigation, an active comparator (open label) and a placebo arm.
- If participants were prematurely taken off the study drug treatment, they were assessed in an end-of-study visit and then discontinued from the study.
- After study completion, it came to light that a large proportion of treatment discontinuations happened to participants in the placebo arm.
- **How should the data be interpreted, in the presence of potential healthy survivor effects?**
- This implies it was not possible to use a treatment policy strategy for treatment discontinuation.
- The primary analysis in the trial used only data from when the participants received the investigational treatment; this is consistent with an analysis targeting a hypothetical or while-on-treatment estimand strategy for the treatment discontinuation ICE.
- It follows that it is important to define the estimand in the study protocol and statistical analysis plan, as this should then lead to a better understanding of whether the chosen method of analysis is appropriate to estimate the estimand of interest.

Example 3: What are possible issues when transitioning a compound between the early phase and late phase teams when different estimands are used?

- During planning for a Phase IIb study, an early-stage team decided to evaluate the treatment effect using as the summary measure the relative change to placebo.
- Another analysis method based on absolute changes on the linear scale could have been specified, as this is aligned more clearly with the recommended regulatory agency approach within the disease area.
- **Within the estimand framework, it is a requirement to clearly state which method is to be used to summarize the treatment effect observed based on the clinical data.**
  - Had the framework been used in this setting, it may have made the proposed analysis choices more transparent at an earlier stage and this could have led to a different choice of summary measure being used.

Estimands and the broader clinical team

- One disadvantage of the ICH E9 R1 addendum is that some think it is only germane to statisticians, as ICH E9 refers to statistical principles in trials.
- Designing clinical trials is a multi-stakeholder exercise.
- Using the estimand framework to specify an estimand and design a study should incorporate views from all relevant stakeholders.
  - At AstraZeneca, we are working towards this goal by presenting on estimands to a wider audience, developing a white paper specifically for early phase trials, and including an estimand section in the protocol template.

References

1. ICH E9 R1 Addendum. (2020, 02 17). EMA. Retrieved from European Medicines Agency website: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf

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