Estimands: Bridging the gap between study objectives and statistical analysis

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I am planning a randomized trial and understand that the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 Addendum (Statistical Principles for Clinical Trials) introduced the concept of estimands to improve the clarity and precision of clinical trial objectives and outcomes. Could you please explain why this is necessary?

1. INTRODUCTION

The concept of estimands emerged as part of a broader effort to improve the clarity and precision of statistical analysis in clinical trials, especially when dealing with complex trial designs. Estimands are quantities that are estimated by statistical analysis.

Randomized controlled clinical trials are considered the gold standard for evaluating the causal effect of an intervention or treatment under study. While it is expected that trials will be designed with balanced risk factors across groups and that participants will adhere to the protocol and complete the study, this is often not the case in practice. As a result, clinical trials face challenges related to missing data, treatment discontinuation, and other intercurrent events (e.g., dropouts or death). These events could complicate the interpretation of trial results, leading to uncertainty about the true effect of treatment. While different statistical approaches have been employed to address these challenges, there was a lack of clear guidance on how to define the treatment effect in such circumstances. In many trials, analyses relied on assumptions about how missing data were handled, which led to inconsistencies across studies. Additionally, while the Intention-To-Treat (ITT) principle is often regarded as the primary approach for evaluating treatment effects in randomized trials, questions remain about whether the estimated effects capture the treatment effects most relevant to clinical and research considerations.

In August 2017, the ICH released the E9 Addendum (ICH E9) titled "Statistical Principles for Clinical Trials," which introduced the formal concept of estimands.[1] The goal was to improve clarity in defining trial objectives, considering intercurrent events and providing a framework for consistently addressing them. The estimand framework was designed to specify the exact quantity to be estimated (the estimand) and to ensure that the trial's objectives, design, data collection, and analyses were consistent with this quantity. It helped clarify the target of inference and distinguished between the estimand (the quantity to be estimated), the estimator (the method used to estimate it), and the estimate (the result obtained from applying the estimator to the data).

The ICH's introduction of estimands was quickly recognized as a significant step toward improving the rigor and transparency of clinical trial analysis. Various regulatory agencies began to endorse the approach, including the FDA, European Medicines Agency (EMA), and Health Canada, among others. Since the final adoption of the ICH E9 (R1) in 2019, the use of estimands has become more common in clinical trial planning, especially for trials involving complex designs.

2. THE DEFINITION OF ESTIMANDS

An estimand is a specific quantity that is to be estimated in a clinical trial. It defines the target of inference (e.g., treatment effect or outcome difference) that the trial aims to measure.[2] The concept of

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DOI: 10.12746/swrccc.v13i54.1415

an estimand also includes a framework that provides a precise description of how the treatment effect is to be estimated. This framework ensures that the trial's objectives, design, and analysis are aligned. This framework addresses how issues like intercurrent events will be handled, ensuring consistency between the trial's objectives and the analysis approach. In short, the estimand defines the precise question that data analysis aims to answer, representing the quantity to be estimated,[3] and the framework guides how this quantity is defined and integrated into the trial process.[4,5]

3. Components of an estimand

Treatment: What are the treatments of interest?

This could include individual treatments or interventions (such as control), as well as combinations of interventions administered concurrently.

Population: What is the population being considered?

This refers to the broader group for which the treatment effect is to be estimated, defining the target population or a specific subgroup that the estimand focuses on. It differs from the "eligibility" criteria in a trial protocol, which specify who can enter the trial based on predefined inclusion and exclusion criteria. It also differs from the analysis set (e.g., all randomized participants) described in the Statistical Analysis Plan (SAP).

Variable/Endpoint: What outcome or endpoint is of interest?

This is the measurable value that directly addresses the clinical question, such as the change from baseline to follow-up, time to an event, or a binary outcome that can be obtained from an individual. It cannot be something like a proportion, which summarizes data across multiple individuals. The variable/endpoint focuses on which endpoint(s) should be estimated, in contrast to the statistical procedures for deriving endpoints described in the SAP. The specification of the variable might include whether there are intercurrent events.

Population-level summary: How will the treatment effect be summarized (e.g., difference in means, odds ratio)?

This refers to a population-level statistic derived from the endpoints of all participants and is used to quantify the overall intervention/treatment effect and to make comparisons between intervention/treatment groups. It is worth noting that the focus of the population-level summary in an estimand defines the treatment effect in the context of the trial's clinical objectives, considering intercurrent events and being closely tied to clinical relevance. In contrast, the summary measures described in the SAP outline the statistical approach for deriving those measures, supporting conclusions based on the analysis.

For example, in a two-arm randomized trial testing whether an exercise intervention reduces HbA1c compared to a wait-list control in an adult obese population, the target population should be adults with obesity who are not taking obesity or diabetes medications. The variable/endpoint would be the change in HbA1c from baseline to post-intervention. The population-level summary would be the difference in the change in HbA1c between the exercise and wait-list groups.

Intercurrent events are events that occur during the course of the study that may affect the outcome or treatment effect. By clearly defining the treatment, population, variable, and how the treatment effect will be summarized, the study design can take into consideration intercurrent events and ensure they are appropriately handled in the analysis.

4. Potential intercurrent events

Intercurrent events related to study intervention/treatment

Events such as treatment discontinuation, dosage adjustments, non-adherence, or the initiation of new

medications that may influence the treatment's effectiveness or the outcome.

Intercurrent events related to changes in outcome measurement

Events like the use of uncertified raters, switching assays, or altering the timing of outcome measurements, all of which can impact the reliability and comparability of the data.

Intercurrent events resulting in missing values

Events such as death or loss to follow-up, which can result in missing data for subsequent time points and affect the completeness of the analysis.

Each of these events needs to be handled carefully when designing an estimand to ensure that the trial's objectives and analyses remain consistent with the intended treatment effect, and that conclusions are not influenced by intercurrent events.

According to the ICH E9 (R1), there are different strategies for handling intercurrent events.[1,7,8] Specifically, each strategy is tailored to address specific clinical questions related to particular intercurrent events. It is important to note that a single strategy does not need to be applied to all intercurrent events. In fact, different strategies are often necessary to accurately reflect the distinct clinical questions associated with each intercurrent event. However, different strategies require consideration of possible bias introduced by the difference in strategy.

5. Strategies for handling intercurrent events

Treatment policy strategies focus on the effect of treatment irrespective of adherence

The treatment policy strategy is a commonly used approach for handling intercurrent events. The key principle is that the outcome is measured and analyzed regardless of whether intercurrent events occur, using all available data for the outcome of interest. This approach aligns closely with the ITT principle often described in SAP, in which all participants are analyzed in the groups to which they were originally assigned, regardless of deviations from the study protocol. However, the treatment policy strategy may not be suitable for terminal events, as values for the outcome variable after such events do not exist.

Hypothetical strategies evaluate the effect under a hypothetical scenario (e.g., if no intercurrent events occurred)

The concept of hypothetical strategies refers to imagining scenarios in which certain events that typically occur in a clinical trial do not happen or occur differently. The purpose is to understand how these events or their absence might affect the treatment outcomes and help inform clinical and regulatory decisions.

In essence, hypothetical strategies are used to simulate how treatment effects might change under different conditions that are not present in the trial but might be relevant in the real world. These strategies help to understand how treatment outcomes could differ if certain events were avoided or occurred differently, offering valuable insights for both clinical decision-making and regulatory assessments. The key is to define these scenarios clearly to avoid misunderstandings about what is being modeled.

For example, suppose that the intercurrent event is the adverse event that leads to treatment discontinuation. Identifying such events is crucial in clinical trials, as they may interfere with the assessment of treatment efficacy. The hypothetical strategy involves imagining two different conditions: a) The subject does not experience the adverse event (so s/he continues the treatment as originally assigned); and b) The subject continues the treatment despite experiencing the adverse event (without discontinuation).

These scenarios are clinically relevant because they attempt to replicate a real-world situation in which a patient might experience adverse events but might also continue treatment or manage the side effects – a common issue in clinical practice, and evaluating

treatment effects in such hypothetical scenarios offers valuable insights.

Composite variable strategies combine intercurrent events and outcomes into a single measure

Composite variable strategies refer to a method used to construct a combined outcome variable that includes information about intercurrent events, within the definition of the outcome. These strategies are employed when an intercurrent event is considered an important part of the outcome, such as treatment discontinuation or death, and its occurrence directly informs the patient's overall treatment success or failure. Specifically, in this strategy, intercurrent events are treated as providing valuable information about the patient's overall outcome. For example, if a patient discontinues treatment due to adverse effects, that discontinuation might be considered as treatment failure. Thus, the outcome variable (e.g., treatment success or failure) could be defined in such a way that discontinuation due to adverse effects is treated as failure, even if the patient didn't formally experience the negative clinical outcome, i.e., failure. Because it involves defining a treatment outcome by combining intercurrent events with the primary clinical outcome of interest, it provides a more comprehensive understanding of treatment effects and reflects the real-world impact of treatments, especially in cases in which terminal events or patient discontinuations are an important part of the overall treatment evaluation.

While on treatment strategies

This strategy refers to focusing on a patient's response to treatment up until the occurrence of an intercurrent event. It places importance on the treatment's effects before the intercurrent event happens. Particularly, if a variable is measured multiple times throughout the trial, only the values up to the occurrence of the intercurrent event are considered relevant. The data after the event is typically excluded, as it may no longer reflect the patient's response to treatment. Alternatively, if a patient dies during the study, the strategy might focus on how the treatment affected the patient while the patient was alive.

In summary, the concept of estimands is expected to continue evolving and to be widely applied in clinical trials around the world. Researchers, regulatory agencies, and pharmaceutical companies are increasingly recognizing the value of clearly defined estimands to ensure that trial results are consistent, transparent, and interpretable. As clinical trials become more complex, estimands will likely improve trial methodology and help ensure that conclusions drawn from trials are reliable and based on clear, well-defined objectives.

Article citation: Yang S, Berdine G. Estimands: Bridging the gap between study objectives and statistical analysis. The Southwest Respiratory and Critical Care Chronicles 2025;13(54):45–49
From: Department of Biostatistics (SY), Pennington Biomedical Research Center, Baton Rouge, LA; Department of Internal Medicine (GB), Texas Tech University Health Sciences Center, Lubbock, Texas
Submitted: 1/8/2025
Accepted: 1/11/2025
Conflicts of interest: none

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