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THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Is there a fundamental rethinking in the way we plan clinical trials? The estimand change in mindset

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Background

- ICH E9 Statistical Principles for Clinical Trials (1998)

> **Intention-To-Treat Principle**
> The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e. the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed and analysed as members of that group irrespective of their compliance to the planned course of treatment.

- In 2010, the National Research Council (NRC) highlighted the need to more clearly distinguish between the target of estimation ("estimand") and the method of estimation ("estimator") in clinical trials.
- While the NRC report on "The Prevention and Treatment of Missing Data in Clinical Trials" focuses on issues arising due to missing data, a framework to coherently align trial objectives and corresponding estimands is important.

Perceived Problems (2014 ICH E9 R1 concept paper):

- Incorrect choice of estimand and unclear definitions for estimands.
- Absence of a framework for planning, conducting and interpreting sensitivity analyses.

Inconsistencies in inference and decision making within and between regulatory regions.

The Estimands Framework: KEY concepts

- ICH E9(R1) Addendum on “Estimands and Sensitivity Analysis in Clinical Trials” released in November 2019
- An **estimand** precisely defines the treatment effect of interest in a clinical trial
  - It defines a population-level quantity that an estimator attempts to estimate and infer based on what is observed in a trial.
  - It has to be aligned with the trial objectives.
  - By exploring different estimands, an assessment of what would have happened under different treatment conditions is possible.
  - It requires defining a population of inference, a variable or endpoint, a specification of treatments, a specification of how to account for intercurrent events, and a population-level summary (statistic) serving as the basis for comparison
- **Intercurrent events** occur after treatment initiation and either affect interpretation of the variable or preclude its observation
  - Discontinuing the experimental treatment
  - Starting alternative treatments before observing the clinical outcome of interest
  - Dying before observing the clinical outcome of interest
- Missing data has to be considered only in the context of an estimand.

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ICH E9 Addendum represents a shift in paradigm

- The estimands framework represents a response to the call to properly inform decision-making. It focuses on:
  - The need to prespecify how the treatment effect is defined under the scientific question of interest linked to the trial objective
  - The concept of intercurrent events and the strategies to address them
  - Aligning estimators/analyses with an estimand
  - Linking sensitivity analysis/estimator to a specific estimand

Implementation of this framework requires close collaboration among study team members of different disciplines and a shift in mindset.