ISCTM Estimands and Missing Data Working Group

20Feb2026 Meeting Minutes from the ISCTM Annual Meeting

Meeting Focus

- Discussion on improving **interdisciplinary collaboration** (clinical, statistical, regulatory) when applying the **estimand framework** in line with ICH E9(R1) and the ICH M11 protocol template.
- Use of **CNS and psychedelics trial examples** to illustrate practical challenges in defining estimands.

Key Discussion Points

1. General Observations on Applying the Estimand Framework

- The estimand framework is conceptually well understood, but in practice, clinical engagement can be limited when the estimand attributes are not specified clearly enough for clinicians to see how they map to the clinical question and trial decisions.
- Greater **structure and clarity** in the requirements for specification of estimand attributes were viewed as essential to facilitate meaningful multidisciplinary input.
- Emphasis on defining estimands in a way that clearly reflects the **clinical question of interest** and intended context of use.

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2. Population Attribute

- The **target population** relevant to the clinical question should be clearly distinguished from the participants enrolled in the trial.
- It was emphasized that defining the population attribute simply "according to the inclusion/exclusion criteria" is **not recommended**, as these criteria describe participant selection rather than the intended treatment population.
- Lack of clarity regarding population representativeness may have downstream implications:

    - If trial participants are not considered representative of the target population, **restrictions in the population description in the product label** may be applied.
- Clear specification of the target population at the estimand level was considered critical for both interpretation of trial results and labeling.

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3. Treatment Attribute

- The importance of specifying the **full treatment regimen** was emphasized, including:
    - Dosage, frequency, route, and duration
    - Relevant background, rescue, or subsequent therapies
    - Allowed and disallowed concomitant medications or therapies
- Clinical input was considered essential for:
    - Defining the treatment regimen (beyond "experimental drug vs control drug/placebo") and understanding how it compares to usual practice and the standard of care
    - Interpreting treatment deviations
    - Determining whether deviations constitute intercurrent events
- It was noted that when treatment is conceived narrowly as "assigned drug vs control drug/placebo," the need for clinical engagement may appear limited; however, when treatment is framed as the full treatment regimen, sustained clinical input is needed to ensure the estimand reflects real-world use and interpretation.
- It was noted that it is often unclear how the estimand specification of the treatment regimen translates into **label language describing clinical trial results**.
    - In particular, when trials primarily estimate the effect of **initiating a treatment regimen**, potentially including the effects of treatment changes or switches when the assigned treatment does not work, this should be clearly reflected in the label sections reporting trial results.

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4. Intercurrent Events (ICEs)

- The importance of **pre-specifying intercurrent events likely to occur in the target population** was emphasized.
- Particular attention should be given to intercurrent events that may **influence the endpoint**.

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5. Intercurrent Event Strategies

- Different intercurrent event strategies were discussed, including the **While on Treatment** strategy.
- It was emphasized that, under a While on Treatment strategy:
    - The **endpoint must reflect the individual-level treatment duration**.
    - The endpoint **cannot be defined beyond the time of occurrence of the relevant intercurrent event**.
- Misalignment between the intercurrent event strategy and endpoint definition was identified as a potential source of interpretational ambiguity.

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6. Population-Level Summary

- Participants noted that the population-level summary is often insufficiently linked to the clinical question.
- The choice of population-level summary should be driven by clinical relevance, such as:
    - Expected outcome
    - Typical outcome
    - Likelihood or probability of achieving a specified outcome
    - Differences in outcomes or events
- Reliance on default statistical summaries without explicit clinical justification was discouraged.

Overall Conclusions

- Effective application of the estimand framework requires **early, structured, and sustained clinical engagement**.
- Clear articulation of estimand attributes is critical to:
    - Align estimands with the clinical question of interest
    - Improve interpretability
    - Support appropriate downstream communication, including product labeling
- Strengthening these linkages was viewed as central to improving interdisciplinary collaboration and ensuring that estimands are fit for their intended decision-making context.