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Panel Discussion

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Estimand

The quantity which is being estimated to address the trial scientific question of interest. The choice of an estimand involves:

- Population
- Endpoint
- Measure of intervention effect.

Example:

Estimand defined by the difference in means versus control for the endpoint in the specified population under the following post-randomization measure of intervention:

- Population: subjects with severe depression
- Endpoint: change from baseline to Week 4 (primary time point) in MADRS total score
- Measure of intervention effect: how to take into account the impact of post-randomization events such as discontinuations – to be specified

Possible estimands

What are the different possible estimands for such a trial?

- Estimand 1: Difference in means versus control for the endpoint defined by:

- Population: subjects with severe depression
- Endpoint: change from baseline to Week 4 in MADRS total score
- Measure of intervention effect: Effect of the initially randomized treatments at Week 4 that would have been observed had all subjects remained on their treatment throughout the double-blind phase.

Data analysis implication: Data after discontinuation should not be included in the analysis of this estimand.

Possible estimands cont.

- Estimand 2: Difference in means versus control for the endpoint defined by:

- Population: subjects with severe depression
- Endpoint: change from baseline to Week 4 in MADRS total score
- Measure of intervention effect: Effect of the initially randomized treatments at Week 4 irrespective of whether some of the subjects may have discontinued treatment prior to the end of the trial.

Data analysis implication: All collected assessments should be included in the analysis, including those after treatment discontinuation. This estimand involves a comparison of treatment policies.

Possible estimands cont.

- Estimand 3: Difference in means versus control for the endpoint defined by:

- Population: subjects with severe depression
- Endpoint: change from baseline in MADRS total score to the last on-treatment observation in the 4-week double-blind phase
- Measure of intervention effect: Effect of the initially randomized treatments on the endpoint.

Data analysis implication: The time point or length of treatment, for which treatment and placebo are to be compared, varies for different subjects. Subjects who remain on their initially randomized treatment contribute data up to the planned end of the treatment period and subjects who discontinue contribute up to their last visit while on treatment. This corresponds to a last observation analysis. Thus, there is no missing data involved using this estimand.

Possible estimands cont.

- Estimand 4: Difference in means versus control for the endpoint defined by:

- Population: subjects with severe depression
- Endpoint: change from baseline to Week 4 in MADRS total score
- Measure of intervention effect: Effect of the initially randomized treatments at Week 4 in subjects who would adhere to their initially randomized treatments throughout the 4-week double-blind phase.

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Question 1

Consider a clinical trial program for the treatment of depression. What is the primary clinical objective of a short-term trial aimed at symptom reduction?

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Question 2

Of the possible estimands, what is the most appropriate estimand to address the primary clinical objective in a short-term depression trial?

Is the choice of estimand dependent on

- stage of the clinical development program (Phase 2 vs. Phase 3 vs. post-approval)?
- stakeholder (regulators vs. prescribers vs. patients/caregivers vs. sponsors vs. payers, etc.)?

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Question 3

What is the most appropriate study design for each type of estimand?