Novartis
Early Development Analytics

Using estimands in PoC studies for infectious diseases: What did we consider?

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BBS Workshop: Estimands in Early Development (ED) across Therapeutic Areas
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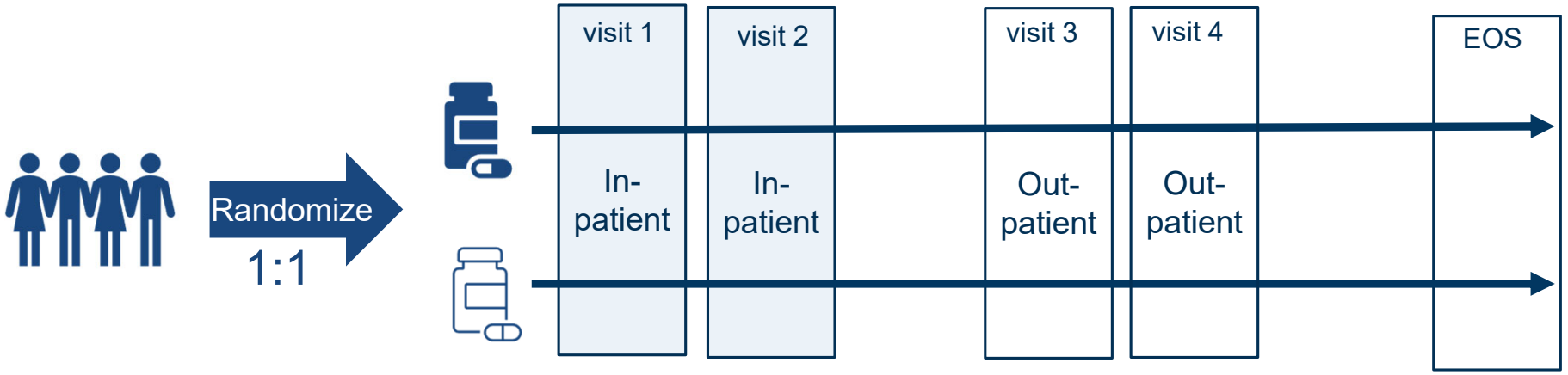
What will I talk about?

1. How were estimands implemented in a Dengue Fever PhIIa trial?
2. How did we adopt the estimand strategy to this early clinical development study?
3. What feedback did we get?
4. What is my view on estimands in early clinical studies?

This talk represents my personal views, not necessarily Novartises views.

Dengue Fever Phlla study: design



- Study design: parallel group, randomized (1:1), controlled, double blind
- Population: adult dengue fever patients
- Specifics: treatment duration beyond in-patient period poses a risk for adherence to drug administration
- Primary endpoint: reduction in viremia

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How were estimands implemented in a Dengue Fever PhIIa trial? Primary estimand

- **The primary clinical question of interest is:**
  What is the effect of the test versus control treatment on viremia reduction at 48 hours post treatment start in patients with dengue fever if treatment discontinuation and interruption had not happened?
- **Primary estimands attributes:**
  - **Population**: Participants aged 18-60 years who have been diagnosed with dengue fever that meet the study inclusion/exclusion criteria.
  - **Variable**: Viremia reduction from baseline at 48 hours post treatment start.
  - **Handling of intercurrent events**:
    - Discontinuation or interruption of study treatment due to any reason within 48 hours post treatment start: Hypothetical strategy
  - **Summary measure**: Difference in mean of viral reduction on log scale at 48 hours post treatment start between test and control treatment.

How were estimands implemented in a Dengue Fever PhIIa trial? Intercurrent event strategy

- Hypothetical strategy used for
  - discontinuation or interruptions of study treatment
  - due to any reason
  - within 48 hours post treatment start
- The interest lies in the treatment effect that would be observed if the event had not occurred i.e. the participant had not discontinued or interrupted study treatment.
- Data handling:
  - data after treatment discontinuation or interruption will be set to missing and imputed using the missing at random (MAR) assumption for both treatment arms.

How were estimands implemented in a Dengue Fever PhIIa trial? Supplementary analysis

- Using a treatment policy strategy to handle intercurrent events.
  - Thus the estimated effect of the intervention here is the effect irrespective of discontinuation or interruption of treatment.
  - Data handling:
    - data after discontinuation or interruption of study treatment will be included in the analysis.

How did we adopt the estimand strategy to this early clinical development study?

- In PhIIa the focus is on the first characterization of the compounds efficacy and safety profile
- The hypothetical strategy is in line with this approach
  - Aiming to reduce the impact of non-adherence to treatment on the results
  - However not omitting the whole participants data but using all data up to the point the event occured.
- Decision of which intercurrent events to consider also reflects there likelihood to be observed
  - Rare events (e.g. deaths) were decided not to be covered upfront.
- Supplementary analysis with treatment policy strategy bridges to a PhIII/ITT type of approach.

What feedback did we get?

- Team's feedback:
  - I don't understand the language you used.
  - Good basis for the discussions on the intercurrent events and how to handle them.
- Statistician's feedback:
  - very helpful concept to discuss specifically the intercurrent events and what to do if they occur transparently. Otherwise the statistician does take the decision how to handle this data maybe without the team's awareness.
  - Fosters more stringent differentiation between which events to handle on the analysis data set level vs. intercurrent event level

What is my view on estimands in early clinical studies?

- Very helpful framework to explicitly discuss
  - Events that impact the data and thus the interpretation of the results
  - and how they are handled
  - in an transparent way.
  - Even if it might require updating the estimand strategy e.g. when learning about new events
- Phrasing the clinical question in estimands is still a learning:
  - Consider «treatment given as planned» vs. «if treatment discontinuation and interruption had not happened».
- Can help to reduce the number of post-hoc requests for different data explorations.