Estimands and Complex Innovative Designs
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Disclaimer

The content of this presentation and other commentary made during this conference are reflective of my own personal opinions and not those of my employer GSK.
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Key Messages

- Principles and thinking process outlined in ICH E9(R1) are relevant whenever a treatment effect is estimated

- ICH E9(R1) therefore remains applicable to CID

- The estimand guides the trial design, not the converse

- Pre-specification in the protocol of potential adaptations and link with estimands is key

- Differentiation between planned and unplanned changes
The Estimand Framework

**Estimand**

- A precise description of the treatment effect reflecting the clinical question posed by the trial objective.
The Estimand Framework

Treatment

Population

Intercurrent events

Population-level summary

Variable

E9-R1_EWG_Step2_TrainingMaterial.pdf (ich.org)
Estimands and CID

First attempt to link the estimand framework and different types of adaptations
- sample size reassessment
- group sequential designs
- enrichment designs

Our proposal is to extend the discussion to other types of innovative characteristics
- Adding or selecting treatment arms
- Modifying the control arm or standard of care
- Adding, selecting, pooling subpopulations
- Bayesian borrowing
Adding or Selecting Treatment Arms

- Example: Platform Trial
Adding or Selecting Treatment Arms

- Example: Platform Trial
Adding or Selecting Treatment Arms

• Platform trials with **several treatment-specific objectives** mean **several treatment specific estimands**
  • Adding an arm = adding an objective = adding an estimand
  • Dropping an arm = dropping an objective = dropping an estimand
  • There are no changes to the original two estimands relative to the initial two treatments
Adding or Selecting Treatment Arms

- How to describe these estimands in the protocol?
- Differences and similarities between the estimands attribute of several treatments for the same disease studied within the platform trial

| estimand attribute          | guidance                                                                 |
|-----------------------------|---------------------------------------------------------------------------|
| A. Treatment                | Different for each treatment investigated but common comparator            |
| B. Population               | Similar for each treatment investigated                                  |
| C. Variable                 | Could vary with the drug as different treatments could target different aspects of the disease (e.g. remission, disease severity, pain...) |
| D. Intercurrent events      | Population-specific IE would be similar (e.g. change in background medication) whereas treatment-specific IE would vary, e.g. positivity to antidrug antibodies (ADAs) |
| E. Population Level Summary | Would change with the variable                                            |
Modifying the Control Arm

- Example: Platform Trial
Modifying the Control Arm

- Example: Platform Trial
Modifying the Control Arm

Can the original estimand still be estimated?

- **Scenario 1**: treatment comparisons of interest are against the current best control
  - Modifying the control arm leads to a new objective and the treatment component of the estimand needs to be modified accordingly
  - Population might change (e.g. ineligibility to new standard of care)
  - New intercurrent events might have to be defined
  - Which analysis becomes (remains) primary, versus Control 1 as initially intended or vs Control 2?

- **Scenario 2**: treatment comparisons of interest are against the control arm, regardless of any changes to the comparator throughout the trial
  - Estimand components needs to refer upfront to a state-of-the-art control therapy
  - All concurrent controls from both Control 1 and Control 2 would be used for the estimation
Adding, Selecting or Pooling Sub-populations

- Example: Basket trial

- Several sub-populations treated independently as separate studies for e.g. logistic efficiency:
  - Sub-populations= independent target populations
  - Separate benefit/risk assessment
  - Separate objectives = separate estimands

- A trial targeting a single homogeneous population:
  - Sub-populations=sub-groups
  - Assessment of consistency
  - Primary estimand would target the overarching population
  - Secondary estimands would be sub-population specific
Adding, Selecting or Pooling Sub-populations

- **Pooling**
  - Primary estimand targets the pooled populations at interim
  - Secondary population-specific estimands remain of interest
  - Data-dependent pooling can induce selection bias

- **Borrowing**
  - Each target population has its own specific estimand
  - A problem of estimation rather than estimand since the treatment effect in Target Population 1 is informed by the treatment effect of Target population 2 and 3
Adding, Selecting or Pooling Sub-populations

- Differences and similarities between the estimands of a given treatment tested in different diseases/subtypes within the same basket trial

| estimand attribute          | guidance                                                                                                                                 |
|-----------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| A. Treatment                | Same for each disease / subtype                                                                                                          |
| B. Population               | Different for each disease / subtype                                                                                                      |
| C. Variable                 | Could vary as the same drug could target different aspects in different populations (e.g., in oncology: OS, PFS, ORR)                      |
| D. Intercurrent events      | Population-specific IEs would be different, whereas treatment-specific IEs would be the same                                               |
| E. Population Level Summary | Would change with the variable and the population (e.g., a same binary variable could lead to percent difference in one population and odds ratio in the other if needed) |
Borrowing of treatment effect

- Example: platform trial
Borrowing of treatment effect

- A careful estimand discussion needs to take place

- Important to ensure the different sources have the appropriate estimand components in common
  - Corresponding adjustments (e.g., for inclusion and exclusion criteria, covariates, or if populations differ) will be required
  - Borrowing information within a trial is less prone to biases than borrowing from external trials, as many aspects of trial conduct are standardized and are less likely to cause bias

- A problem of estimation rather than estimand
  - e.g. implementation of a Bayesian hierarchical model

- Importance of supplementary estimands and sensitivity analyses, e.g. with and without non-concurrent controls
Other types of innovative characteristics

- Sample size reassessment
- Change to randomisation ratio
- Early stopping for overwhelming efficacy
- Early stopping for futility

- Would not be linked to any changes to the estimand
Other types of innovative characteristics

- Change of primary endpoint

- Coprimary endpoints
  - First occurrence of a major adverse cardiovascular event
  - First occurrence of death from cardiovascular causes or hospitalization for heart failure

- Because of lack of funding, the study could not enrol the expected number of participants therefore coprimary endpoints changed to more sensitive endpoint in order to make up for loss of power

- New primary endpoint
  - total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure

- Estimand component should be updated

- Difference between planned vs unplanned changes
Conclusions

• **Estimand framework is applicable to any study in which a treatment effect is estimated**
  - This applies to complex innovative designs
  - Estimands guide the trial design, not the converse
  - Pre-specification in the protocol of potential adaptations is key

• **Difference between planned vs unplanned changes, e.g. COVID19**
  - Change in population
  - New intercurrent events
  - Treatment landscape, e.g. new standard of care
  - Can the original estimand still be estimated?

• **Estimation**
  - Data-dependent selection of estimands poses additional challenges to define reliable estimators, confidence intervals, and hypothesis tests
  - Bias associated with the selection of estimands is closely related to the problem of multiplicity testing

• **Engagement with regulators via e.g. Scientific Advice is paramount**
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