The estimands framework in non-inferiority trials: Past, Present & Future

Sunita Rehal, GSK,

on behalf of the EIWG sub-team on estimands in non-inferiority trials

12 June 2023

Disclaimer

Disclaimer:

The views expressed by the presenter are not necessarily the views and practices of their employers, or of any of the EIWG member companies.

Acknowledgements

- Helle Lynggaard (Lead of EIWG NI sub-team, Novo Nordisk)
- David Wright (AstraZeneca)
- Vivian Lanius (Bayer)
- Marian Mitroiu (Biogen)
- Amel Besseghir (ClinChoice)
- Florian Lasch (EMA)
- Chrissie Fletcher (GSK)
- Sunita Rehal (GSK)
- Oliver Keene (KeeneONStatistics)
- Christoph Helwig (Merck)
- Brennan Kahan (MRC CTU at UCL)
- Tobias Muetze (Novartis)
- Chien-ju Lin (Roche)
- Qing Wang (Roche)
- Claudia Hemmelmann (Sandoz Inc.)
- Susmit Sekhar (Sandoz Inc.)

Outline

- Introduction to non-inferiority trials.

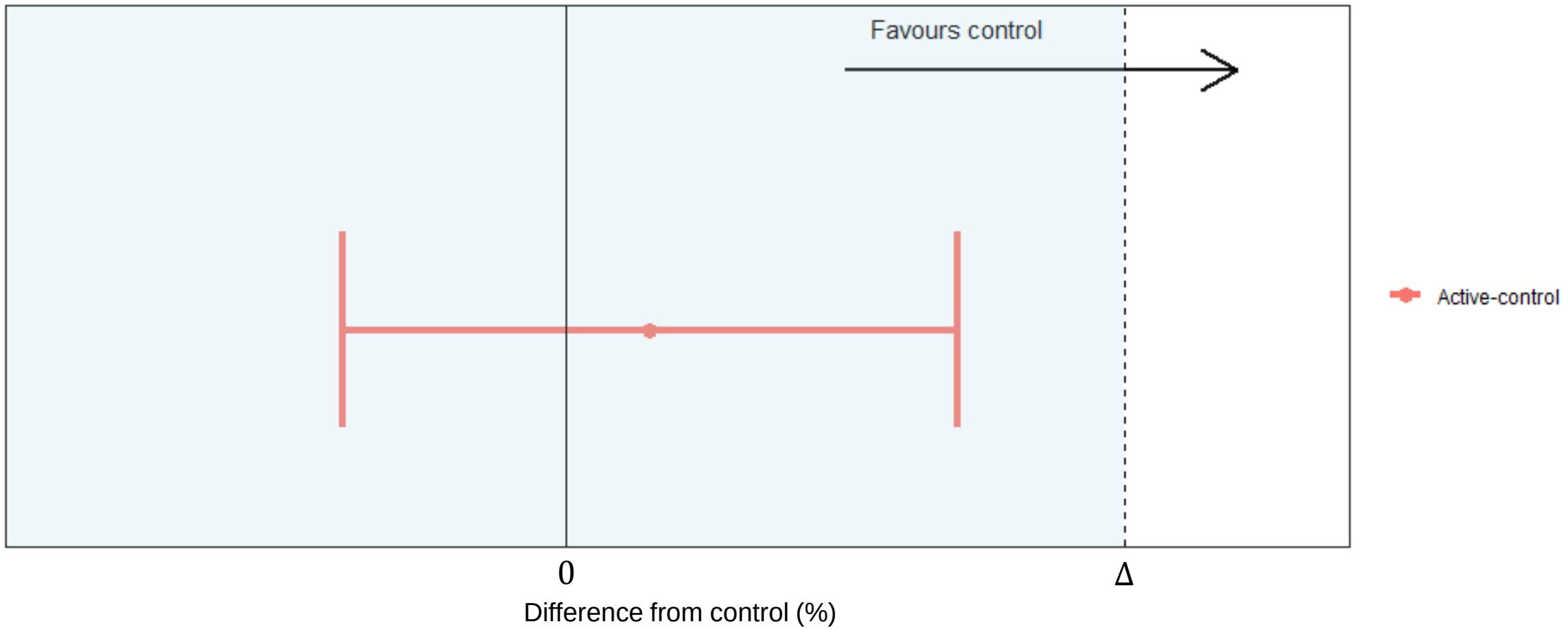
- Past:
  - What was being estimated pre-ICH E9(R1)?

- Present:
  - Realisations, considerations & discussions given ICH E9(R1) (2019).

- Summary.

- Future:
  - What's next.

Introduction to non-inferiority



Past

Two analysis sets to determine non-inferiority

- Full analysis set (following the intention to treat principle)
  - “Anti-conservative”.

- Per-protocol set
  - Can be biased in either direction.
  - Difficult to state what the treatment effect is targeting.

Two analyses - one clinical objective!

Present

Application of the estimands framework for non-inferiority

- Analysis set:
  - "The treatment effect of interest should be defined in a way that determines the population of subjects to be included in the **estimation and the observations from each subject to be included in the analysis considering the occurrence of intercurrent events.**"
- What does the full analysis set and per-protocol analysis estimate?
- Address two very different clinical questions.
- Start with the clinical question!

ICH E9(R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (Effective in EMA 30 July 2020)

ICH E9(R1) addendum on non-inferiority

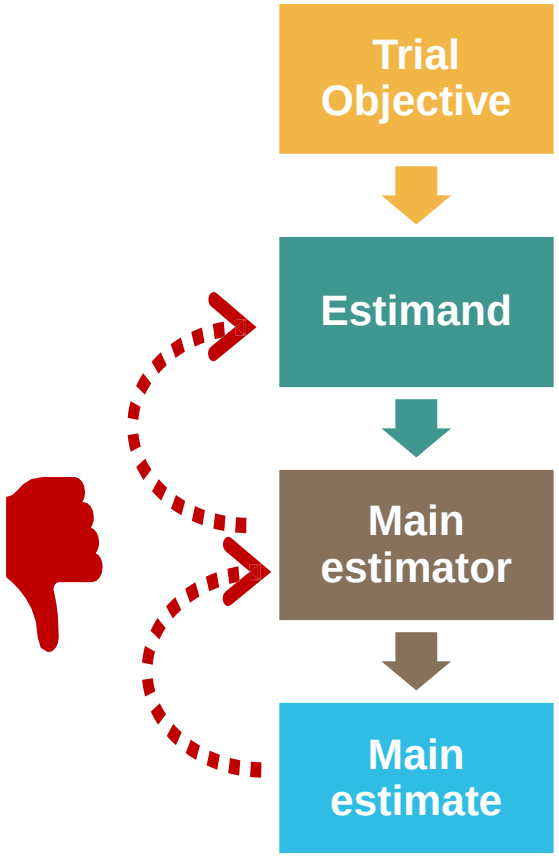
"Per-protocol analysis is subject to severe bias." "…in a way that is less biased and more interpretable than naïve analysis of the per protocol set."

"…it may not be possible to construct a relevant estimand to which analysis of the PPS is aligned."

"…the use of a treatment policy strategy (which would correspond to analysing **using the full-analysis set under the ITT principle** described in ICH E9) **is generally not conservative,** since responses in both treatment groups can appear more similar after intercurrent events."

ICH E9(R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (Effective in EMA 30 July 2020)

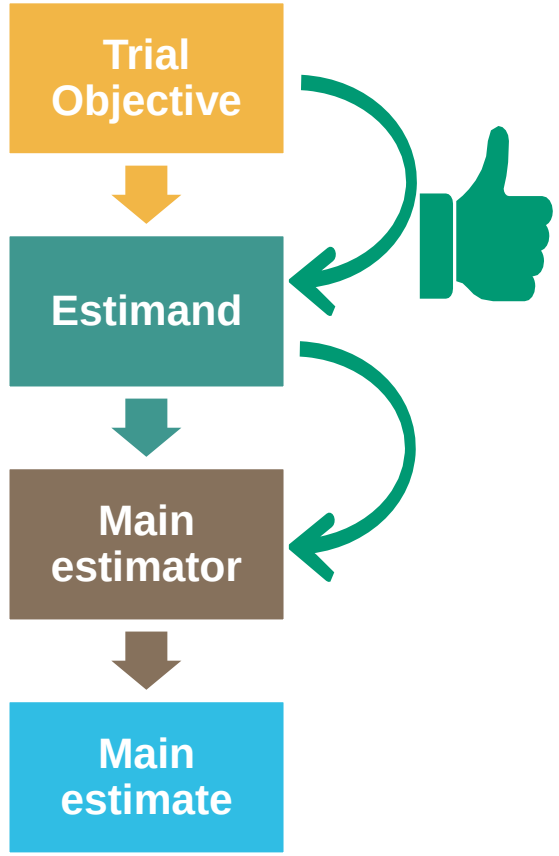
Conservativeness and analysis sets



- Not aligned with the thinking of the estimand framework.
  - No longer thinking about the clinical question.
- Estimator driving the estimand.
  - Thinking about the analysis result.
  - Opposite of what the addendum seeks to do.

Thinking about the clinical question

- Impact on treatment effect of chosen strategy important.
  - E.g. For a NI trial, intercurrent event rescue medication taken.
    - Handled using treatment policy strategy to reflect real-world setting.
    - If more patients on the treatment arm took rescue medication compared with the reference arm, would stakeholders accept the clinical relevance if NI was (or was not) demonstrated?
    - And if more patients on the reference arm took rescue medication compared with the treatment arm would stakeholders accept the clinical relevance if NI was (or was not) demonstrated?



What about “per-protocol”…?

- What does per-protocol mean?
  - In practice ill-defined, usually in relation to data/analysis and often subjective.
  - “Adherence to the protocol.”
    - Attended all follow up visits & collected outcomes?
    - Took treatment as prescribed?
    - Compliance to % doses?

- “Per-protocol analysis” does not target a relevant estimand.

- No handling strategy that excludes outcome measures.

Must be clear what is being estimated.

Other important discussions

Important considerations for non-inferiority trials

Defining two estimands

- Is this needed given two analyses were required by regulators pre-ICH E9(R1)?
  - If it is clear what is being estimated then perhaps unnecessary requirement.
  - Supplementary estimand may be considered depending on the study.

Testing for superiority after non-inferiority

- Can the same estimand be used?
  - The hypothesis changes, but what about the estimand?
  - Unclear and under discussion within the group.

Important considerations for non-inferiority trials

Margin

- Determining the margin relies on evidence from previous studies.
  - Historical control information.
  - Information on intercurrent events not reported pre-addendum in the way that is now expected.

- How should historical control information from the margin be incorporated given the framework?
  - Some information would be available in publications (e.g. CONSORT flow chart).
  - Otherwise discussions in teams of what would be a sensible estimate.

Estimation of estimands for non-inferiority studies

- Do the assumptions behind methods used for superiority trials hold for non-inferiority?
- Other methods? E.g. using causal inference methodology?

Summary

- As for superiority trials:
  - Apply the thinking process of the estimands framework in non-inferiority trials.
  - Define one primary estimand and consider adding a supplementary estimand.
  - Any of the strategies may be relevant to handle intercurrent events.
  - The relevance of the clinical question should drive choice of the handling strategy.

- Specific to non-inferiority trials:
  - Testing for superiority after demonstration of non-inferiority.
    - Careful consideration if one common estimand can be defined.
  - Choice of NI margin should reflect the estimands in historical trials.

Future

What will non-inferiority trials look like in future?

- Learnings taken from regulatory interactions.
- Lots to do!
- Over time, information on intercurrent events will be available and included when determining the margin.
- Estimation methods for non-inferiority trials.

Paper to come!