Non-inferiority and the Estimand Framework

Helle Lynggaard, Novo Nordisk,

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

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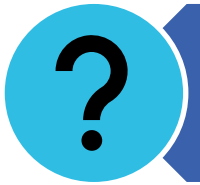
Agenda

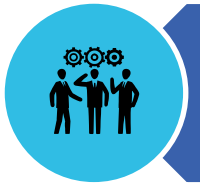
Fundamental questions for non-inferiority trials post-ICH E9(R1)

Assay sensitivity and the estimand attributes



Can we answer the fundamental questions?

Communication of results



Summary

Fundamental questions for non-inferiority trials post-ICH E9(R1)

Combining past and present

Q1	Q2	Q3	Q4
• Can we use the same estimand for non-inferiority and superiority objectives?	• Do we need to reflect the thinking behind the FAS and PPS analyses in the estimand • e.g., by defining co-primary estimands?	• Are we still supposed to do a traditional per protocol analysis?	• How do we  trials?

FAS: Full analysis set; PPS: per protocol set

ICH E9(R1)

Q1 and Q2:

*An **estimand** can be constructed to target a treatment effect **that prioritises sensitivity to detect differences** between treatments, if appropriate for regulatory decision making.*

Q1 and Q2:

*Estimands that are constructed with one or more intercurrent events accounted for using **the treatment policy strategy present similar issues for non-inferiority** and equivalence trials as those related to analysis of the FAS under the ITT principle.*

ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS
TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

Q2 and Q3:

*In respect of the framework presented in this addendum, **it may not be possible to construct a relevant estimand to which analysis of the PPS is aligned.***

Q3:

***Estimands** might be constructed, with aligned method of analysis, that **better address the objective** usually associated with the analysis of the PPS. If so, analysis of the **PPS might not add additional insights**.*

FAS: Full analysis set; PPS: per protocol set; ITT: intention-to-treat

EMA guideline on diabetes trials (2024)

Q1 and Q2:

For active controlled trials with a non-inferiority (NI) hypothesis, ***the same primary estimand strategy*** *as outlined above might be justified.*

Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus

Q2 and Q3:

Furthermore, it is ***likely necessary that a supplemental estimand is specified*** *to address the impact of important intercurrent events like protocol violations and deviations*

New EMA guidance

EMA concept paper on non-inferiority guidance (February 2024) - objectives

The putative placebo comparison to demonstrate efficacy of the new treatment

The assessment of the benefit relative to the comparator (e.g. for additional claims),

The intention to demonstrate that the new treatment is not harmful (non-inferior safety vs. placebo)

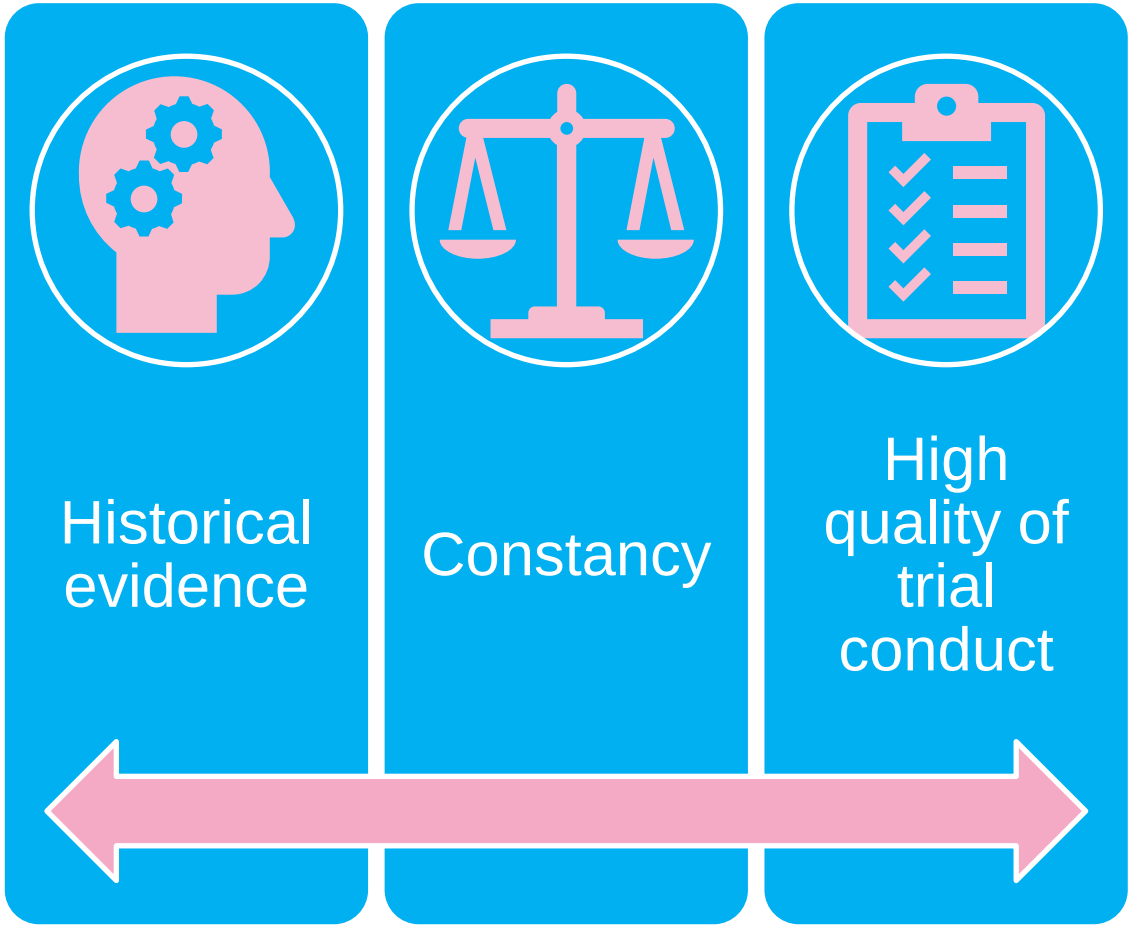
Q1 and Q2: ***"[…] it is important to target an estimand adapted to the specific setting of a non-inferiority […] comparison."***

Assay sensitivity

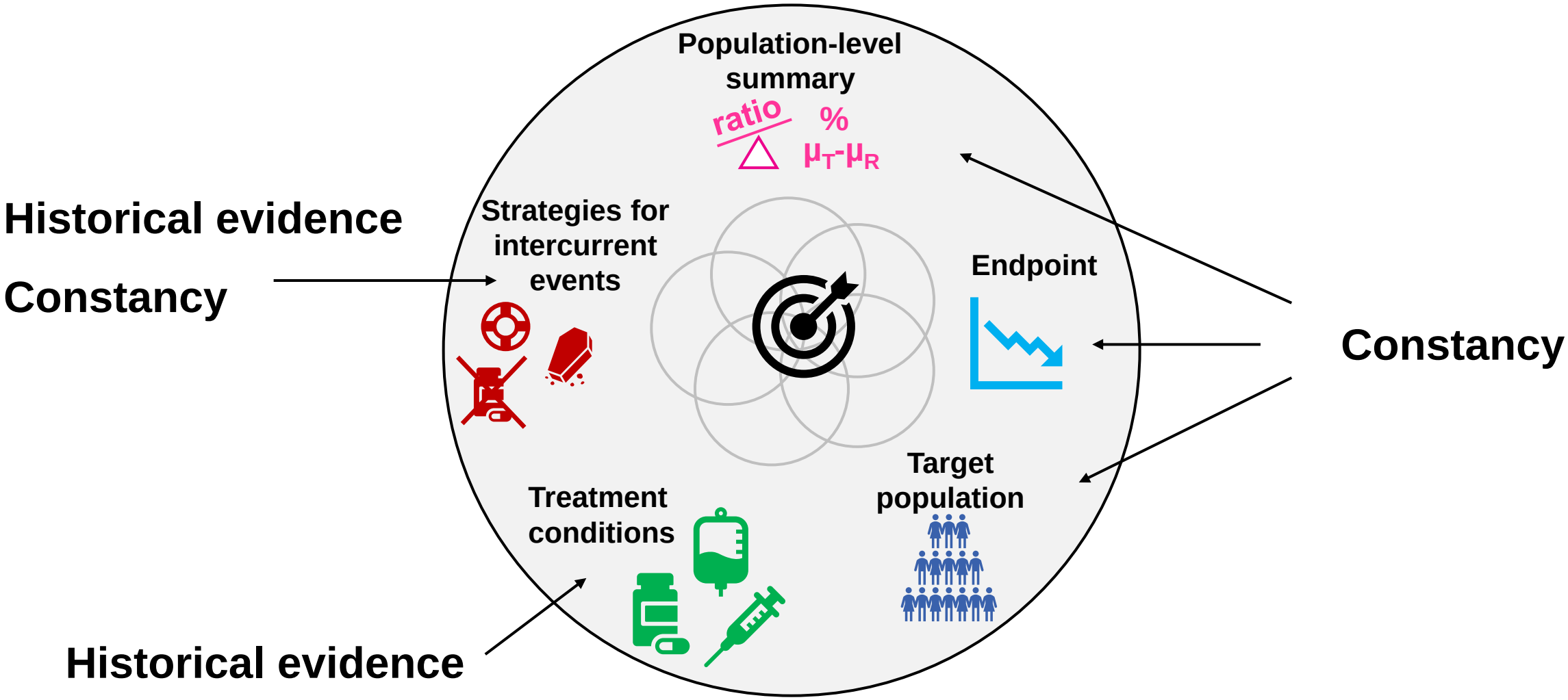
ICH E10 (2000), FDA guidance Non-inferiority clinical trials to establish effectiveness (2018)

CHOICE OF CONTROL GROUP AND RELATED ISSUES IN CLINICAL TRIALS

"a property of a clinical trial defined as the ability to distinguish an effective treatment from a less effective or ineffective treatment."



Assay sensitivity and the estimand attributes are linked!



Estimands cannot be conservative!

An estimand can be constructed to target a treatment effect ***that prioritises sensitivity to detect differences*** *between treatments, if appropriate for regulatory decision making.*

ICH harmonisation for better health

Addendum on Estimands and sensitivity analysis in clinical trials

To the guideline on statistical principles for clinical trials

ICH E9(R1)

Non-inferiority to be demonstrated for both FAS and PPS.

PPS perceived to be more sensitive to detect differences by excluding protocol deviations

Unfortunate terminology:

- ”a conservative estimand”

The estimand is the ”truth” we are trying to estimate

Is the estimand relevant in the given setting?

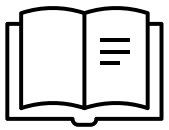
20 November 2019

FAS: Full analysis set; PPS: per protocol set

Q1: Same estimand for non-inferiority and superiority objectives?

Simple!

- Non-inferiority to be shown for both FAS and PPS
- Superiority to be shown for FAS



Addendum on Estimands and sensitivity analysis in clinical trials

To the guideline on statistical principles for clinical trials

ICH E9(R1)

20 November 2019

We begin with thorough discussions of step 1 of the thinking process

- May lead to
  - Same estimand, likely different estimators, or
  - Different estimands, generally different estimators.

Will lead to a more complex communication!

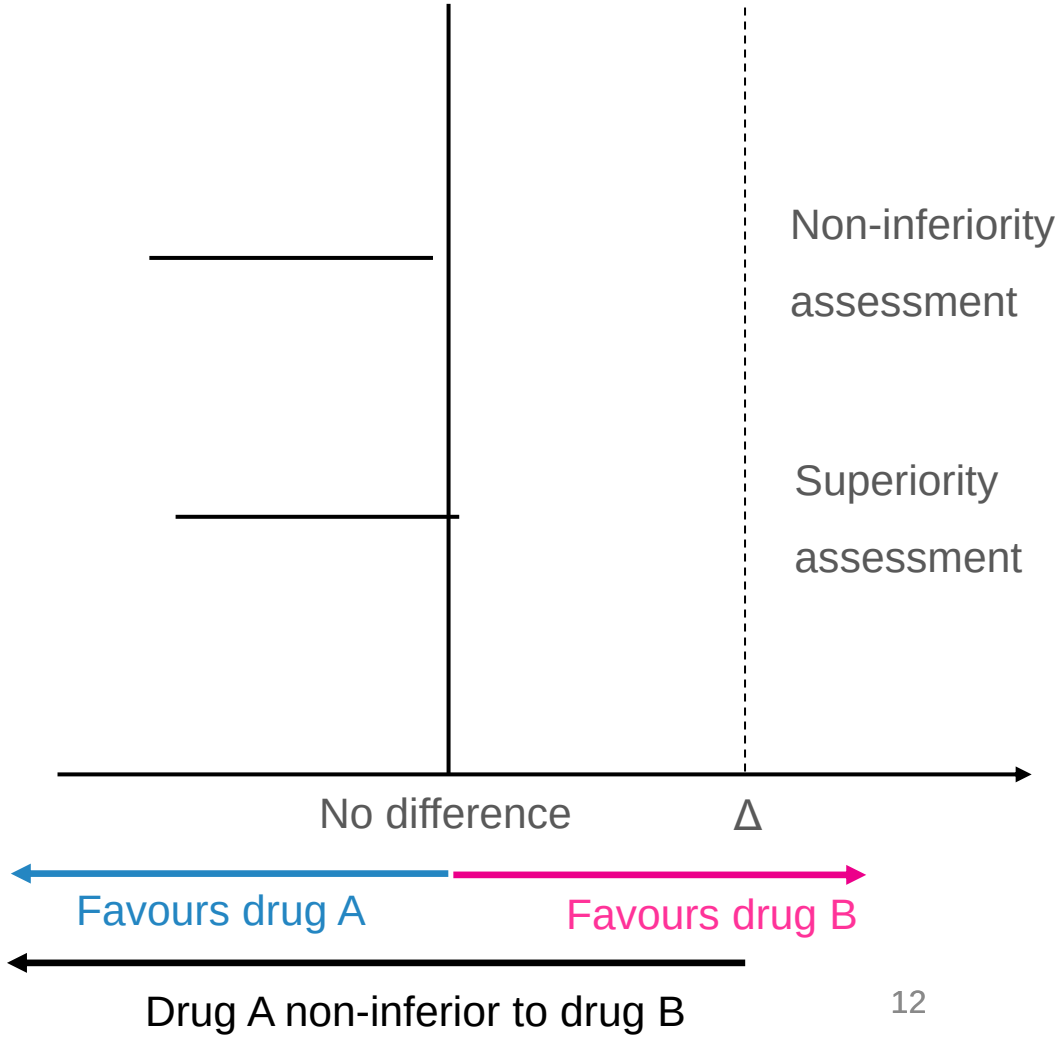
FAS: Full analysis set; PPS: per protocol set

Complex communication: Toy example – weight management

Different estimands for non-inferiority and superiority objectives

- **Non-inferiority:** What is the difference in means between change from baseline to week 68 in body weight in patients with obesity, treated with drug A versus drug B **as though** patients never discontinue treatment and **as though** rescue therapy is unavailable?

- **Superiority:** What is the difference in means between change from baseline to week 68 in body weight in patients with obesity, treated with drug A versus drug B **irrespective of** treatment discontinuation and use of rescue therapy **as needed**?



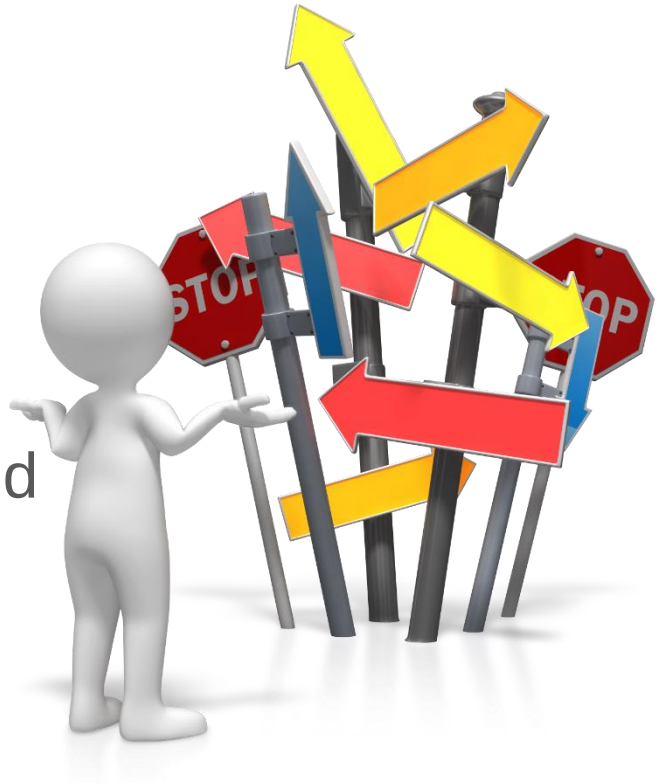
Q1: Same estimand for non-inferiority and superiority objectives?

Contradicting guidance?

- ICH E9(R1) and EMA concept paper:
  - probably not
- EMA guidance on diabetes trials:
  - probably
- Depends on the specific non-inferiority objective and the clinical setting?

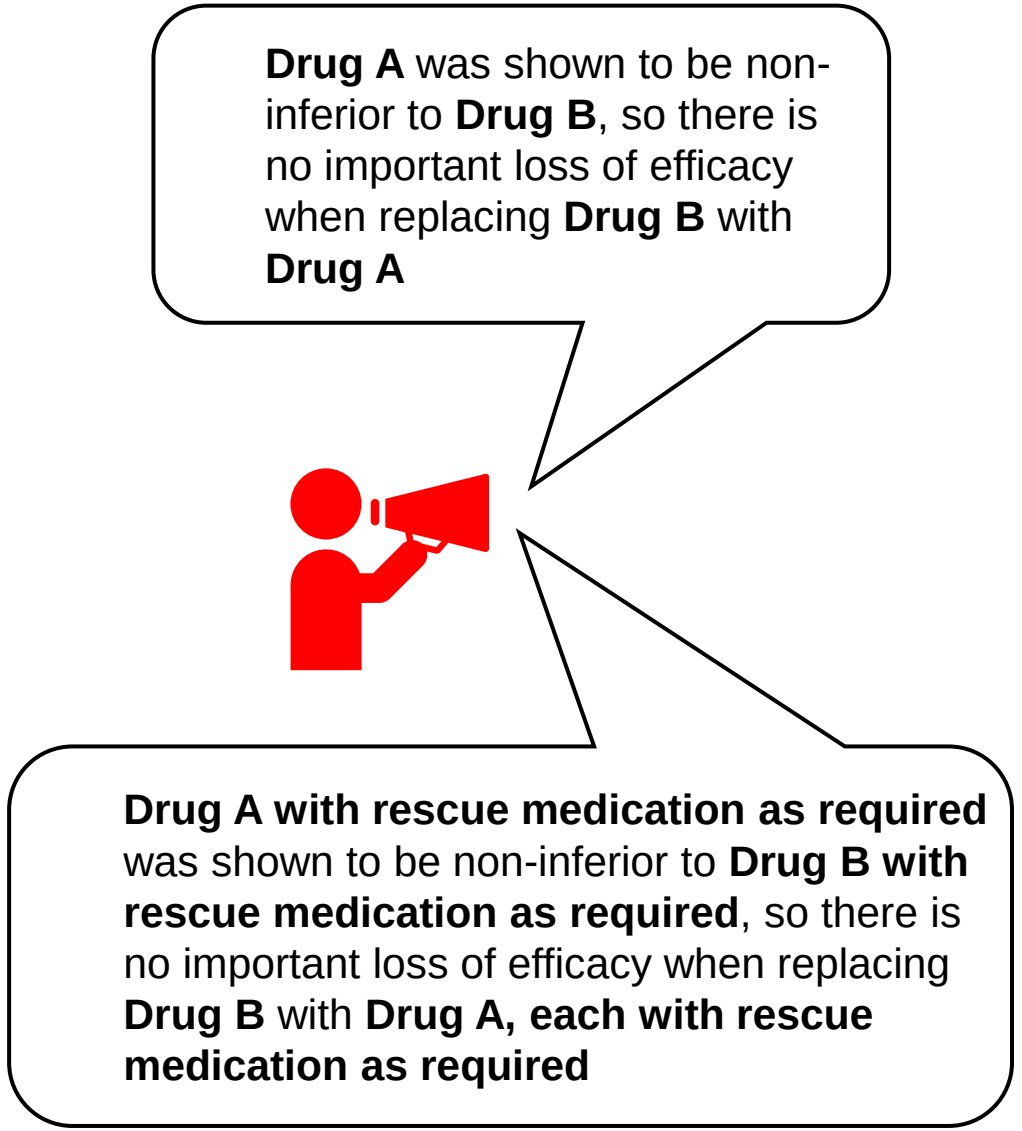
Q2: Reflect the thinking behind FAS and PPS analyses?
Q3: Role for PPS analysis?

- Common approach: all intercurrent events are handled by
  - treatment policy strategy - FAS analysis
  - hypothetical strategies (or principal stratum strategy) - ”PPS” analysis
- Pre-ICH E9(R1):
  - FAS did often not reflect the true ITT principle
  - PPS removes randomised participants due to protocol deviations
- Do not define two co-primary estimands to bridge to the old thinking, or to get better assurance on the non-inferiority conclusion
  - Consider what is relevant in your trial
  - Consider adding supplementary estimands



Communication of results – precise language is imperative!

- Results:
  - Clear context
    - Clarify estimand and intercurrent events distribution
  - Non-inferiority assessment followed by superiority assessment:
    - Clarify if the same estimand was used
    - Clarify if the same estimator was used
- Conclusions:
  - Reflect the precise objective and the estimand
- Proper communication of results includes adequately describing the estimand in the label



Summary

Q1: Same estimand for non-inferiority and superiority?

- Likely to depend on specific non-inferiority objective and clinical setting.
- Carefully consider if the same estimand can be defined for both objectives.

Q2: Co-primary estimands?

- Not only to reflect the thinking pre-ICH E9(R1).
- An estimand cannot be said to be conservative
  - Discuss which question is relevant in each specific setting.
- Embrace the estimand thinking!

Q3: Need to do a traditional PPS analysis?

- No.
  - The estimand framework has clarified the limitations of a traditional PPS analysis; such analyses appear to have no continued role in evaluating trials.

Never provide an estimated treatment effect or conclusions without information on the estimand

Concise language needed!


THANK
YOU

References

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