Draft EMA Non-inferiority guideline: Opportunities and Challenges

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Presentation based on the comments from EIWG sub-team on estimands in non-inferiority trials

Members from Estimand Implementation Working Group (EIWG) sub-team on non-inferiority trials (www.eiwg.info)

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Disclaimer

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Agenda

Key aspects of the draft guideline

Areas where further clarification or guidance would be helpful

Key aspects of the draft guideline

Key aspects of the draft guideline (1)

Objectives (e.g., absolute efficacy or relative efficacy) of non-inferiority comparisons are clearly distinguished

Estimands are central to many aspects of non-inferiority comparisons

- They affect affect assay sensitivity and choice of margin
- No expectation to default defining two co-primary estimands
- Directly linked to constancy assumption

Key aspects of the draft guideline (2)

Protocol and clinical study report should include clear description and justification of non-inferiority margin and assay sensitivity

The definition of “conservative” applies to the estimator, not to the estimand

Per-protocol analysis set should no longer be used for primary or secondary analyses

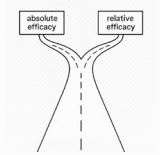
Aspects where additional guidance would be helpful

Overview of additional guidance that would be helpful

Next slides highlight some aspects where additional guidance would be helpful

- Based on comments from EIWG sub-team on estimands in non-inferiority trials

Focus on four aspects

- Target audience 
- Absolute vs relative efficacy 

- Constancy assumption: assessment and violations 

- Communication of results 

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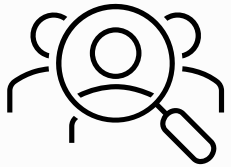
Who is the target audience?



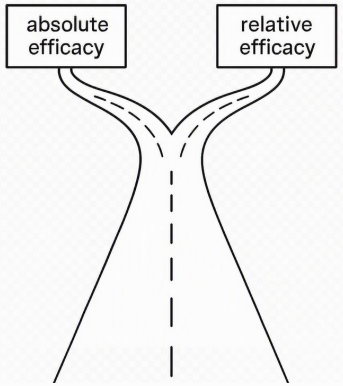
Guideline seems to target mainly statisticians, but has significant implications for clinicians and medical writers

Key areas require multidisciplinary input

- For example, estimand, assay sensitivity, non-inferiority margin, constancy assumption

Clear, non-technical explanations in key sections could help reaching all stakeholders

Absolute vs relative efficacy: clarification needed



Draft guidance states that "absolute efficacy should be performed before a test of relative efficacy"

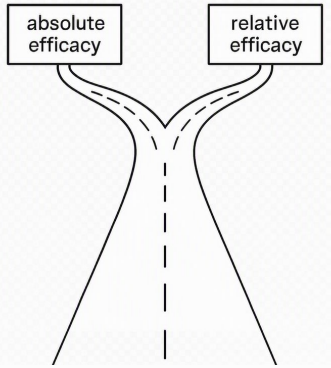
- Both can be tested simultaneously if the non-inferiority margin is strict enough

Unclear decision framework for use of absolute and relative efficacy, including their role in

- Regulatory conclusions
- Benefit-risk evaluation

Clarification on the roles of the two objectives would help sponsors align study objectives and analysis strategies with regulatory expectations

Absolute vs relative efficacy: an example where absolute efficacy is not possible



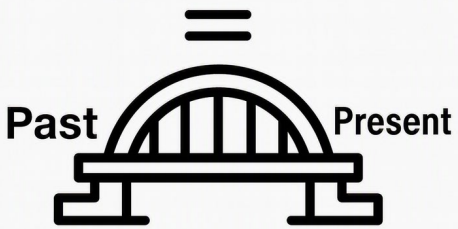
Relevant historical placebo-controlled evidence is needed to support the margin used to establish absolute efficacy through non-inferiority comparison

In some indications (e.g., insulin-replacement in type 1 diabetes), such evidence may be unavailable or ethically infeasible because placebo would withhold essential treatment

- Non-inferiority comparison may support relative efficacy but may not establish absolute efficacy

Guidance could clarify the acceptable approach, regulatory implications, and documentation requirements when absolute efficacy cannot be adequately evaluated

Operationalizing the assessment of assay sensitivity and the constancy assumption



Lack of assay sensitivity may render a non-inferiority comparison uninterpretable

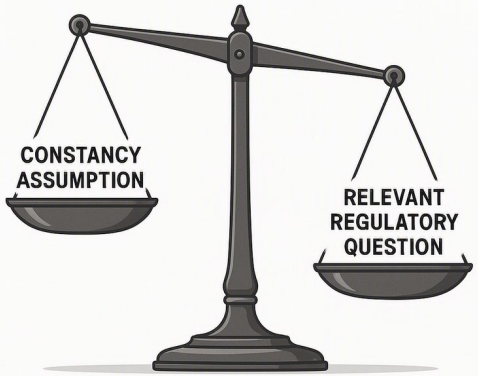
Assay sensitivity is strongly linked to the credibility of the constancy assumption

Draft guidance suggests that assessment of assay sensitivity should be pre-specified in the protocol and included in the clinical study report

Guidance could clarify which factors are expected to be comparable when assessing the constancy assumption, including through examples

- Many factors may affect the constancy assumption, including estimand, trial quality, study population, standard of care, comparator dose and implementation, concomitant treatment, adherence, rescue medication, follow-up duration and endpoint assessment

When is a non-inferiority comparison uninterpretable?



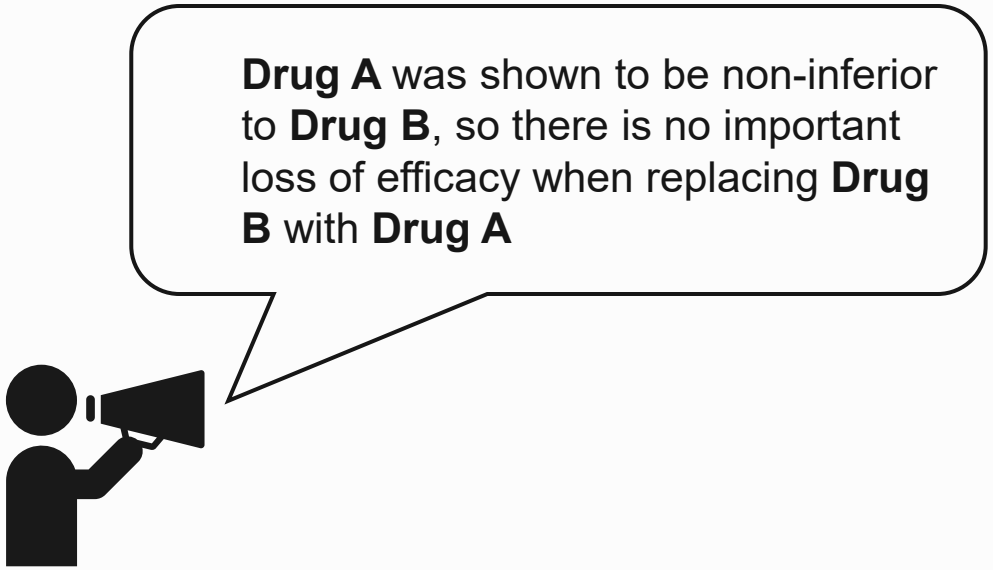
Estimand is key part of the constancy assumption

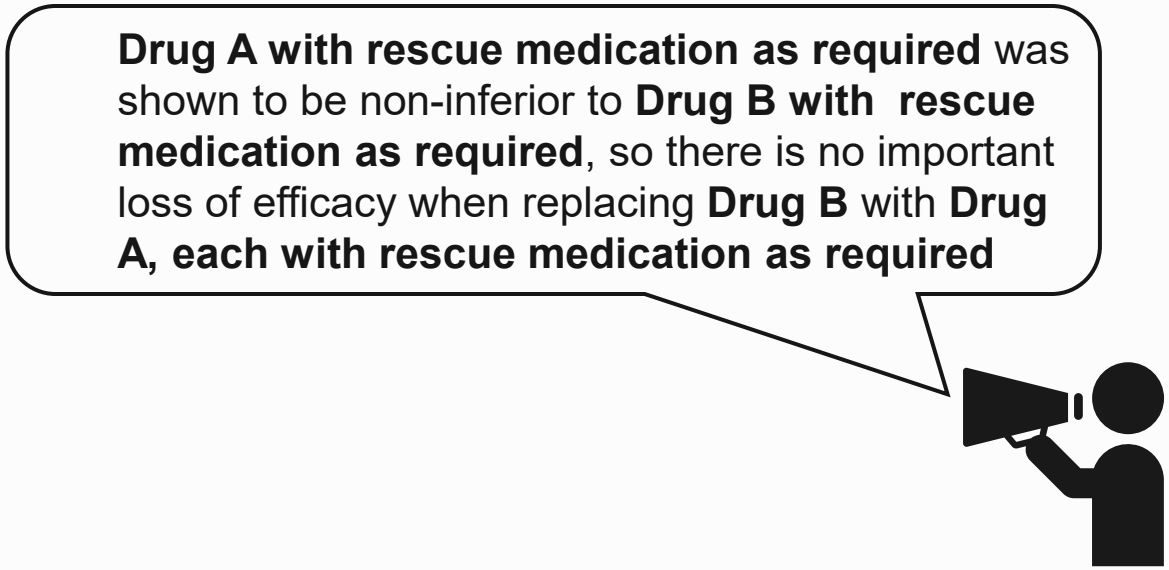
Draft guidance highlights that priority might be given to relevant regulatory question over constancy assumption

- Estimand in new non-inferiority trial might differ than the one from historical studies, leading to violations of the constancy assumption
- Requires assessing its impact on the ability to conclude absolute efficacy

Further clarification, including examples of how to assess the impact of differences on the constancy assumption would help sponsors determine which analyses and documentation are needed

Communication of results: non-inferiority of what?





Stating more clearly the nuances of the non-inferiority conclusions would set expectations about precise and transparent interpretation and communication of trial results

Summary and conclusion

Overall valuable and well-developed guideline

Important and timely update

- It is a strong step forward, particularly in the implementation of estimands

Guideline would benefit from broader accessibility

Further clarification and guidance would be beneficial in several key areas, including…

- communication of results,
- operationalizing the assessment of assay sensitivity, and
- assessment of violations of the constancy assumption