Considerations when Selecting Strategies for Intercurrent Events in Non-inferiority Trials

On behalf of Estimand Implementation Working Group (EIWG) Non-inferiority Subteam

Sue McKendrick[a], Helle Lynggaard[b], Sunita Rehal[c] and **David Wright[d]**

Affiliations: a) PPD™ Clinical Research Services, Thermo Fisher Scientific, UK; b) Novo Nordisk A/S, Denmark; c) Statistics and Data Science Innovation Hub, GSK, UK; d) BioPharma Early Biometrics and Statistical Innovation,Data Science & AI, BioPharmaceuticals, Cambridge, UK. R&D, AstraZeneca

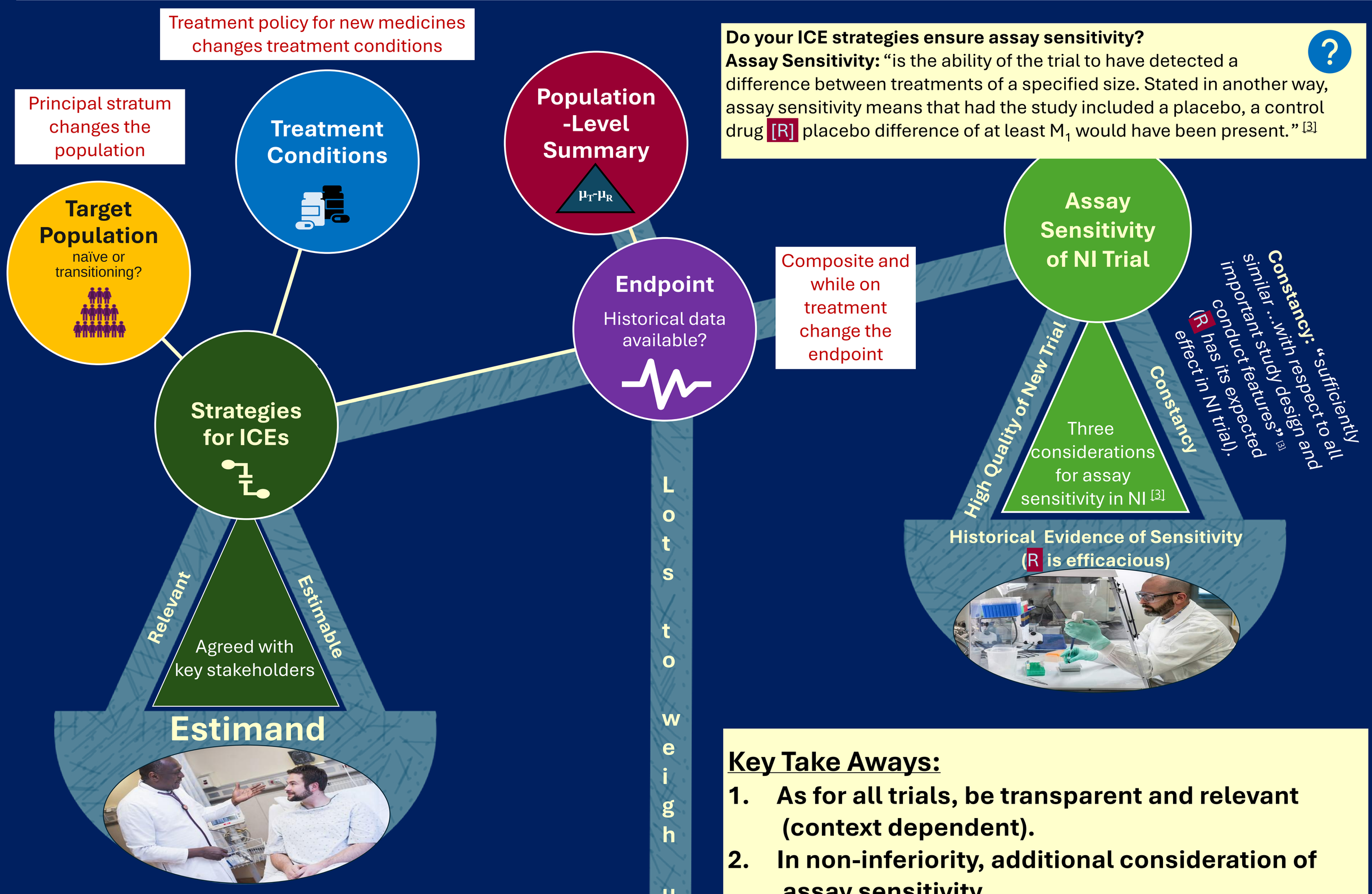
Poster Objective: Estimands[1] for non-inferiority goals is an evolving area particularly in the light of the Committee for Medicinal Products for Human Use (CHMP)'s recent concept paper[2]. This poster aims to highlight some of the issues and considerations in applying the estimand framework.

Therapeutic Setting and Intent of Treatment Determining a Non-Inferiority Trial Objective: Let's consider a situation where we have developed a new test (T) medical entity in the same in class as a reference product, R, but expected to have some added benefit in convenience, cost and/or safety. It is unethical to run a trial to compare T with placebo and so the goal is to show no important loss of efficacy if T was to be administered rather than R, i.e., within a pre-defined non-inferiority (NI) margin [3]. In the historical trial for approval of R, patients who discontinued treatment for tolerability or lack of efficacy were transitioned to a prohibited interacting medicine and withdrawn from the trial. No estimand was declared – is it possible to retrospectively define it? Analysis was via a mixed model for repeated measures (MMRM) so that missing data were predicted by the MMRM. New medicines have since been approved.

Consider the Strategies to Handle these Intercurrent events (ICEs): in designing a trial to show NI of T to R, which strategies follow from the objective

Engagement Exercise: given the historical context above, please add three pins (one strategy for each ICE) that best follow:

Intercurrent Event/ Strategy	Treatment Policy	Hypothetical	Composite Variable	While on Treatment	Principal Stratum
Discontinuation of treatment					
Use of new approved medicine					
Use of alternative medicine (prohibited in historical trial)					



Do your ICE strategies ensure assay sensitivity?

Assay Sensitivity: "is the ability of the trial to have detected a difference between treatments of a specified size. Stated in another way, assay sensitivity means that had the study included a placebo, a control drug [R] placebo difference of at least M_1 would have been present." [3]

Key Take Aways:

1. **As for all trials, be transparent and relevant (context dependent).**
2. **In non-inferiority, additional consideration of assay sensitivity.**
3. **Additional recommendations in [4]**

External Validity in a Changing Clinical Landscape

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References:

[1] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials E9(R1). Published 2020. Accessed August 23, 2024. E9 (R1) Step 5 addendum on estimands and Sensitivity Analysis in Clinical Trials to the guideline on statistical principles for clinical trials (europa.eu)

[2] Committee for Medicinal Products for Human Use (CHMP). Concept paper for the development of a guideline on non-inferiority and equivalence comparisons in clinical trials. Published 2024. Accessed August 08, 2024. https://www.ema.europa.eu/en/documents/scientific-guideline/concept-paper-development-guideline-non-inferiority-equivalence-comparisons-clinical-trials_en.pdf

[3] Food and Drug Administration (FDA), "Non-Inferiority Clinical Trials to Establish Effectiveness," 2016, https://www.fda.gov/media/78504/download.

[4] Lynggaard H, Keene ON, Mütze T, Rehal S. Applying the Estimand Framework to Non-inferiority Trials. Pharmaceutical Statistics (2024). https://doi.org/10.1002/pst.2433

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