The future of per protocol set analyses in non-inferiority trials

EFSPI regulatory statistics workshop
10-12 September 2025

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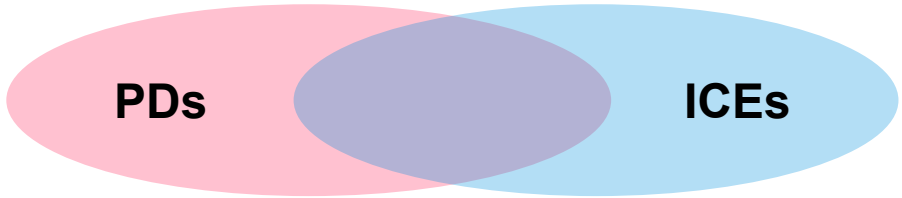
Problem statement

- Phase 3 non-inferiority study
  - Estimand framework implemented
    - Hypothetical strategy to address most intercurrent events (including premature treatment discontinuation and intake of prohibited medication)
  - No per protocol set (PPS) defined and no PPS analysis planned

- Uncertainty about the need for a PPS analysis in a non-inferiority setting
  - Estimand view → no PPS needed
  - Traditional view → for non-inferiority trials, PPS more conservative than FAS
  - Regulatory view → ?

- Protocol deviations (PDs) and intercurrent events (ICEs)
  - PPS: exclude patients with important PDs and/or ICEs?
  - Some PDs might not impact efficacy
    - For the sake of discussion: many of those expected



Relevant guidance and literature (not exhaustive)

- EMA Points to consider on switching between superiority and non-Inferiority (2000)
  - "[…] FAS and PPS have equal importance […]"
- ICH E9 (R1) addendum (2020)
  - General role of PPS analyses revisited ("[…] whether the need to explore the impact of protocol violations and deviations can be addressed in a way that is less biased and more interpretable than naïve analysis of the per protocol set […]")
- Lyngaard et al. Applying the Estimand Framework to Non-Inferiority Trials. PharmStat. 23:1156-1165 (2024)
  - "The estimand framework has clarified the limitations of a PPS analysis and such analyses appear to have no continued role in evaluating [non-inferiority] trials."
- EMA Concept Paper for the Development of a Guideline on Non-Inferiority and Equivalence Comparisons in Clinical (2024)

Questions to the panel

1. Given the estimand framework and the known limitations of the PPS approach, should sponsors nonetheless plan for a PPS analysis in future non-inferiority studies?

2. From a regulatory perspective, are there alternative analyses that sponsors should consider pre-specifying to effectively address the questions that the PPS analysis aims to answer?

Acknowledgements:
Thanks to Andrea Schulze, Bohdana Ratitch, and Thomas Schmelter for helpful discussions on this topic.

Health for all, Hunger for none

Thank you!

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