



Meta-analyses and the estimand framework

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Acknowledgement

Topic inspired by discussions in the EFPIA/EFSPI Estimand Implementation Working Group (EIWG), and aspects of this will be discussed at the PSI Annual Conference 2024

Motivation

- ICH E9(R1): *“[...] in situations when synthesising evidence from across a clinical trial programme is envisaged at the planning stage, a suitable estimand should be constructed, included in the trial protocols, and reflected in the choices made for the design of the contributing trials. Similar considerations apply to the design of a meta-analysis, [...]”*
- Conducting a meta-analysis where trials are aligned according to an overarching estimand would:
 - Increase transparency in trial selection
 - Decrease between-trial heterogeneity (increase external validity)
 - Facilitate clearer interpretation of meta-analysis results

Where guidance is needed

- To what extent should estimand attributes be aligned across trials?
 - Specifically, target population and treatment conditions are likely to deviate across trials
 - Also, the definition and frequency of events is likely to change over time
- What overarching interest is beyond the actual trial?
 - For example, a strategy may imply very heterogeneous treatment regimes across studies (e.g., medication and standard-of-care are likely to change over time)
- What level of evidence is required for a pivotal meta-analysis?
 - Specifically, should more than one "meta-analysis estimand" be defined in the protocols, e.g., one primary and one or more supplementary estimands

Call for an update to reflect the estimand framework of CPMP/EWP/2330/99, POINTS TO CONSIDER ON APPLICATION WITH 1. META-ANALYSES; 2. ONE PIVOTAL STUDY