Adaptive Designs – an HTA Perspective

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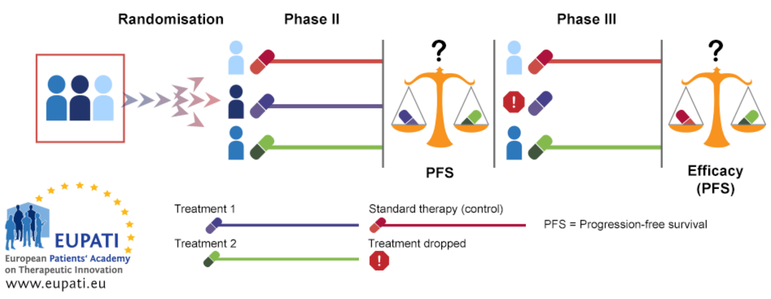
Adaptive trials can provide the same certainty of results as traditional RCTs, provided they are conducted under the same key methodological principles.

Example:

Seamless Phase II/III design



Evaluation of certainty of results should be determined by:

- **Internal validity** (extent to which a study is free from bias) and results are **RELIABLE**
- **External validity** (extent to which study results can be generalized to the target population) and results are **RELEVANT**
- **Statistical precision** (uncertainty associated with study results due to random sampling variability) and results are **ROBUST**

Confirmatory Adaptive designs (primary scope of draft ICH E20 and aligned with HTA Guidance on Validity of Clinical Studies):

- **Adaptation rules should be clearly defined in the protocol** with clear descriptions of estimands and analysis methods accounting for the pre-specified adaptations
- In seamless Phase 2/3 adaptive designs, patients from phase II continuing to phase III should satisfy phase III eligibility criteria and **aligned to the target population**
- **Type I error should be strictly controlled**
- **Impact of adaptations** on study characteristics should be assessed (e.g. changes in population or bias in treatment effect estimates due to adaptations)
- **Provide clear documentation** summarising how the study was conducted including assessing potential biases (using the Cochrane Risk of Bias Tool in HTA submissions)

Key considerations for Indirect treatment comparisons (ITCs), which include adaptive design trials:

- Treatment effect estimates in adaptive designs **can be subject to biases** due to planned changes in key design elements and **should be corrected for at the study level**
- Matching-adjusted indirect comparison (MAIC) and simulated treatment comparison (STC) can be used to **correct for potential bias in treatment effect estimates** when there are differences in effect modifiers between studies e.g. **differences in patient population due to adaptations** involving enrichment or changes in inclusion criteria.
- **Sensitivity analyses are needed** to assess key assumptions and other potential biases e.g. homogeneity of treatment effects, treatment selection at interim analysis.

Conclusion

- There is **alignment between HTA agencies and regulatory agencies on key methodology principles** important for adaptive designs which enable reliable, relevant and robust estimates of treatment effects to be generated for decision making.
- **Treatment effect estimates** in adaptive designs trials **can be subject to biases** due to planned changes in key design elements and **need to be carefully evaluated**.
- **Bias correction methods should be implemented at the study level** before conducting ITCs which include estimates of treatment effects from adaptive designs
- **Provide clear documentation** showing adaptive designs were pre-specified and potential biases are carefully evaluated in reporting results for HTA using the Risk of Bias tool

References:

HTA CG Guideline on Validity of Clinical Studies: https://health.ec.europa.eu/publications/guidance-validity-clinical-studies-joint-clinical-assessments_en
Draft ICH E20 Adaptive Designs: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e20-guideline-adaptive-designs-clinical-trials-step-2b_en.pdf