EUROPEAN FEDERATION OF STATISTICIANS IN THE PHARMACEUTICAL INDUSTRY
Representing Statistical Associations in Europe

# Complex clinical trials, enabling innovative designs

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Acknowledging input from many industry colleagues

# Two topics - common themes

**Trials need not be "complex"**. But modern treatment modalities / strategies often are.

**Regulatory requirements for a trial might not be what patients look for**.

- Multiple estimands needed to describe effect. How to pick the one to define "trial success" and design trial around?

**Estimation methods for many problems exist.**

- They make assumptions.
- Can criteria be developed that guide tradeoffs between assumptions?

- **Type I error control**:
  - What alternative metrics would be appropriate?
  - What gaps are there that need to be addressed to be able to give such guidance?

# Complex treatment strategies, patient's journey studies

Stakeholders and what they want from a clinical trial (think of PFS – OS in oncology, open-label):

- **Regulators**: Easily interpretable effect for initially randomized treatment. Proven long-term effect.
- **HTA**: Easily interpretable long-term effect.
- **Patients in the trial**: Option to cross-over after progression, otherwise high risk for them to leave trial.
- **Patients**: Concerned about enrolling in trials with perceived inferior control arm and no option of crossover after progression.

**How can Regulators and Sponsors collaborate to navigate that conundrum?**

# External controls, Bayesian methods

- Regular regulatory feedback: RCTs are feasible / ethical, even when **sponsor's intel suggests patients would not be willing / available**.
  - ECAs, Bayesian borrowing, extrapolation / bridging and other innovative designs could help address feasibility challenges.
  - How to facilitate better pressure-testing of extent to which alternatives to RCT could provide acceptable quality evidence in these situations? Kit Roes: *"We also have the challenge of being able to quantify and compare the level of evidence between alternatives better".*
- Existing guidance: single arm and externally controlled trials.
- Gaps: Guidance on
  - **Role of augmented control:** hybrid randomized / externally controlled trials.
  - Bayesian borrowing / integrated evidence / meta analysis in a confirmatory setting.
  - Room for deviating from minimizing bias / maximum type I error rate control in a confirmatory setting?
    - If so under what circumstances?
    - What alternative metrics would be appropriate for evaluating designs in such circumstances? Average type I error? Optimising tradeoff between type I and type II errors?
    - What gaps are there that need to be addressed to be able to give such guidance?
- Questions also relevant for **master protocols**.

# Proposal to foster progress

Joint workshop(s).

- **NOT**: discussion of “pros- and cons” – scientific literature provides these and that does not lead us anywhere.
- **RATHER**: develop framework along the above common themes (tradeoffs between assumptions; tradeoffs between type I and II errors), to enable objective evaluation of alternatives to standard RCTs.