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

Beyond Randomized Controlled Trials (RCTs)

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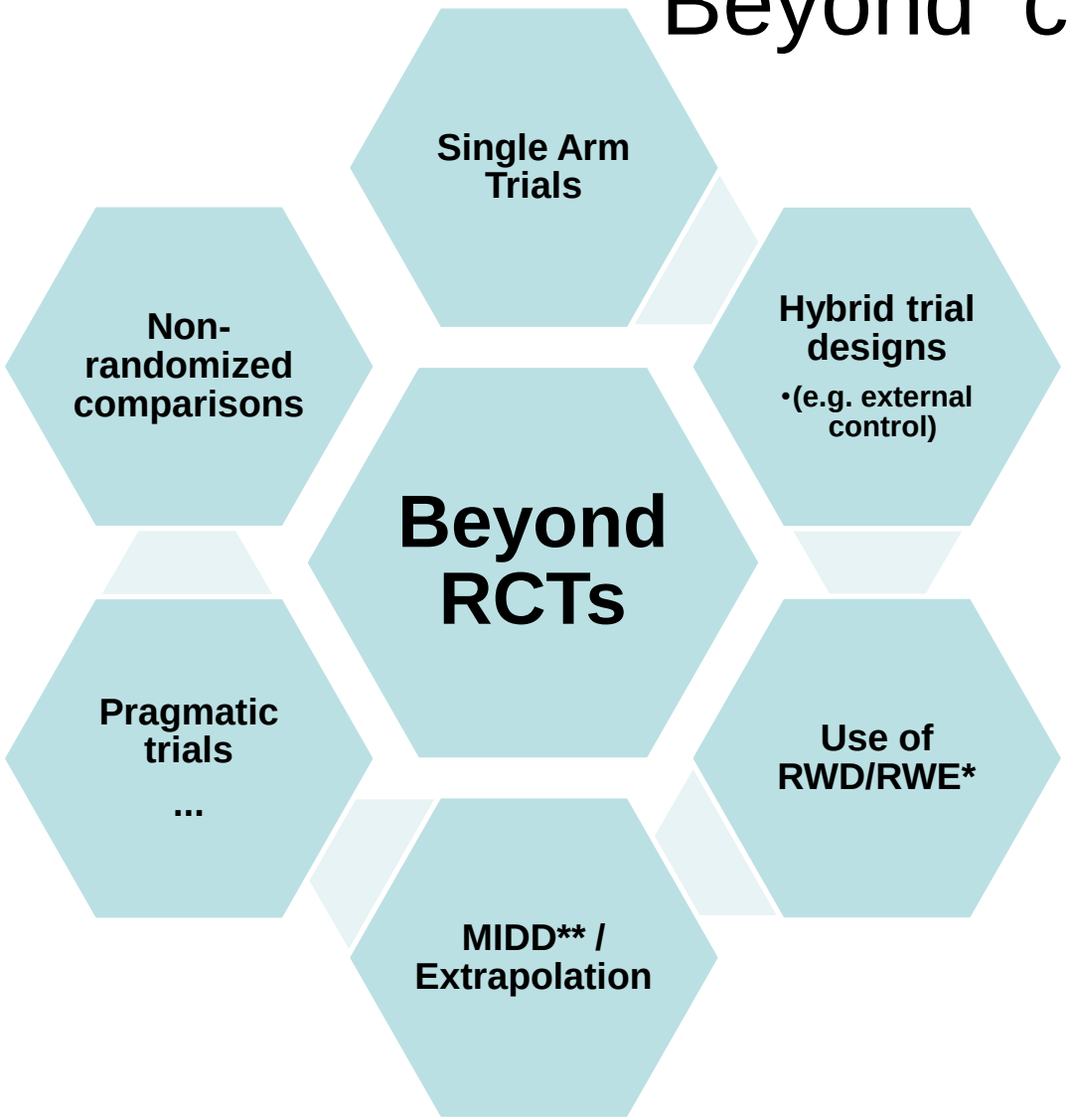
Acknowledging input from many colleagues;
Inspired by a presentation given by Robert Hemmings

Beyond ‘conventional’ RCTs



- RCTs are the gold-standard for evidence generation
- A ‘beyond RCT’ approach seems to be considered if
  i. Evidence generation through RCTs is not feasible AND
  ii. It can provide fit-for-purpose evidence
- ‘Feasibility of an RCT’ assessment is often based on a complex trade-off
  - ‘RCT to assess: Does smoking kill?’ vs ‘RCT to meet unmet clinical need in a rare disease’
- **Can we focus on:** When can ‘beyond RCT’ approaches provide fit-for-purpose evidence for primary proof of efficacy?

* Real World Data / Real World Evidence
** Model-Informed Drug Development

Why are RCTs gold-standard for evidence generation?

- A RCT enables estimation of the causal effect of treatment assignment
- Causal effect based on RCT:
  - How does the outcome of trt assignment compare to what would have happened to the same subjects under alternative assignment?
- RCT + mild assumptions imply: association = causation

R

- Randomization of patients to different trt arms
- Allows like-with-like comparisons
- Reduces selection bias and confounding

C

- Internal control arm
- Allows comparison of outcomes between groups that are treated with different therapies

T

- Trial = experiment
- Ideally with pre-specified, built-in quality measures, e.g. blinding; same assessments and procedures for all patients

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When can ‘beyond RCT’ approaches provide convincing evidence?

The GOOD

- Needed where RCTs face ethical and practical challenges
- Can help answer questions which cannot be addressed by RCTs
- Methodological advancements for design and analysis tailored to ‘beyond RCT’ setting increase reliability of evidence on causal effects

The BAD

- Loose protection against certain biases
- Need more (untestable) assumptions to justify association=causation
- Share many challenges for evidence generation that observational trials face

(Challenges widely discussed in literature + regulatory guidance documents)

What is needed to make progress?

1. **Structured framework** for evaluating the acceptability of a particular 'beyond RCT' proposal, considering the associated trade-offs
   - Critically assess what role certain design, data collection and analysis features play
   - See MIDD credibility framework
2. **Case studies** illustrating what good looks like, in terms of
   - Acceptable trade-offs
   - Suitable clinical trial methodology