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

Complex clinical trials – Session 2 Platform Trials

EMA ACT-EU workshop
Amsterdam, 23th November 2023
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Acknowledging input from industry colleagues & EU-PEARL discussions

Confirmatory Platform Trials: Why at all?

- **Indication focus vs. compound focus**
- **Operational efficiencies: Site start-up, common protocols**
- **Statistical efficiencies, where…**
  - it is hard to recruit study participants
  - it is hard to get the relevant endpoint data
  - there is an unmet medical need without appropriate control
- **Aim:** Allow faster & better informed decisions
- **How to achieve this:**
  - Sharing of control data, adaptive decision making, optimized allocation

Problem statement – Concept paper

"Aim is to describe under which concrete circumstances and methodological constraints platform trials are suitable for regulatory decision making"

EMA concept paper on platform trials targeting

1. **Type I error control**

2. **Design characteristics that increase uncertainty in treatment effect estimates**

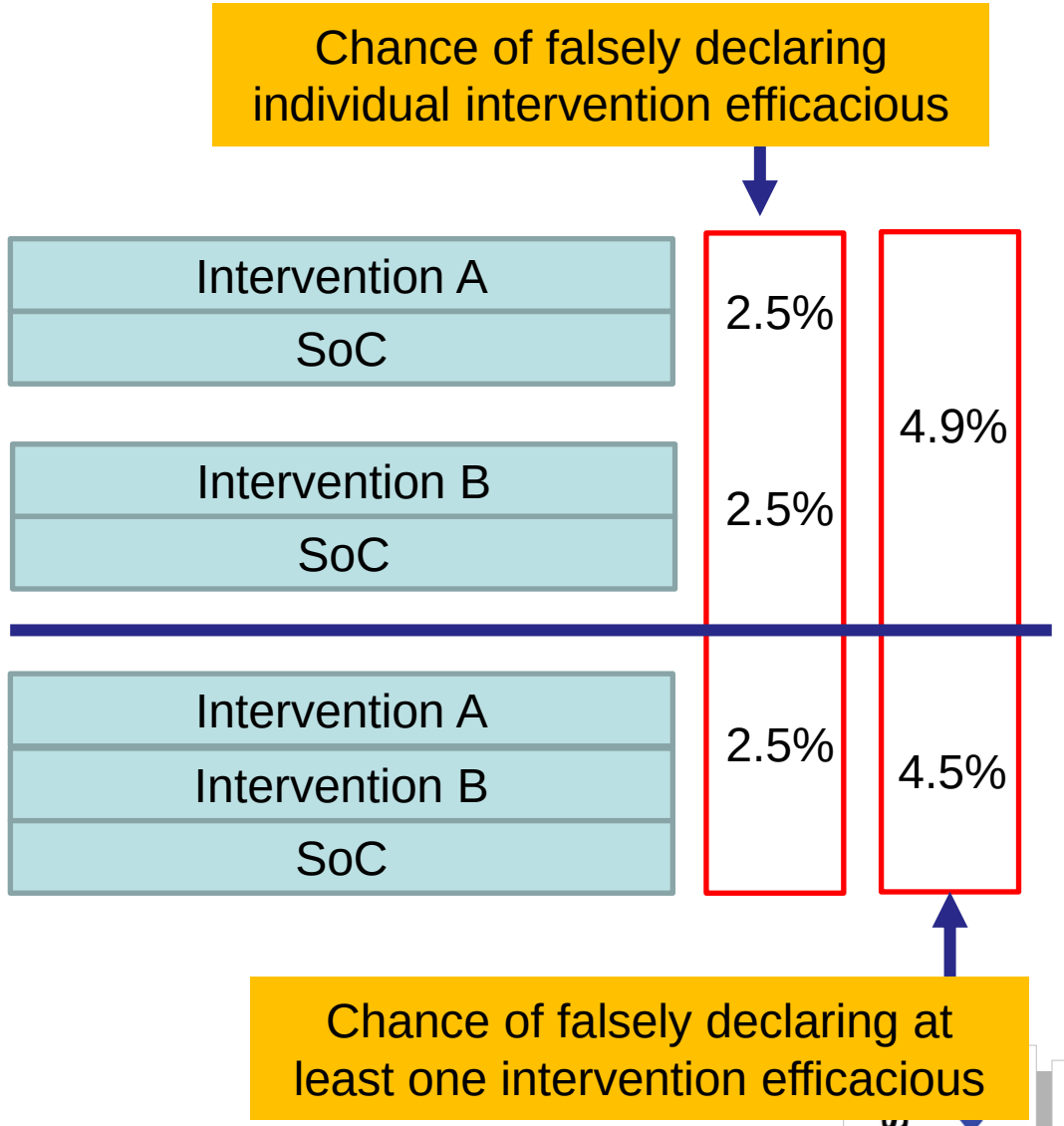
3. **Bias**

Type I error control

"Inferentially independent hypotheses"

- What does this mean?
- Does "intervention owner" matter?
- "Inferentially dependent" hypotheses provide opportunity to use techniques like Bayesian hierarchical models
- Should same "success rules" apply to all arms?
- Which other error concepts, such as "Bayesian average type-1 error", would become relevant?

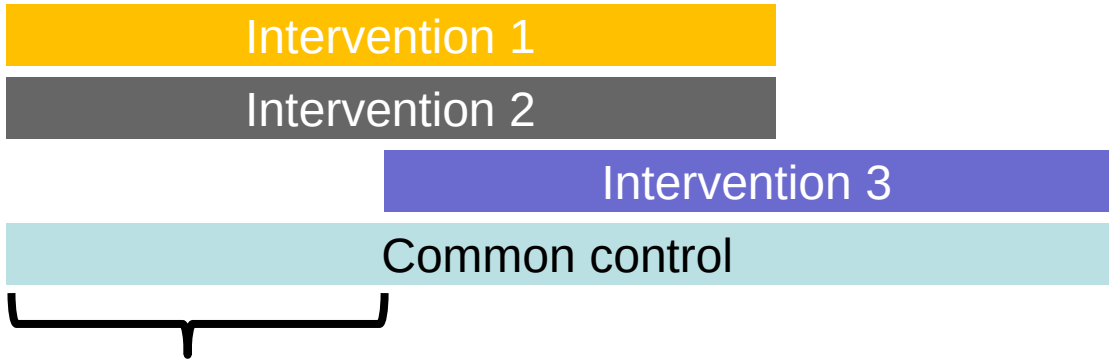
Guidance required on when which type of error rate control shall be implemented.



Uncertainty in treatment effect estimates

Choice of control group:

- When is it appropriate to include non-concurrent controls?
- What operational/statistical design consideration would support inclusion of non-concurrent control data?
- How to handle different routes of administrations for the same control?
- How to change the control group?



Non-concurrent controls for intervention 3

Adaptive change of allocation ratio:

- ~50% of platform trials use response adaptive randomization → What to consider for confirmatory trials?

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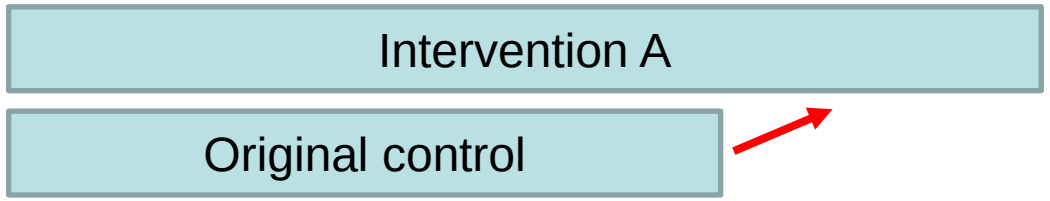
Oncology:
patient switching to intervention



Resulting comparison:

"Intervention A" vs. "Delayed intervention A"

Non-concurrent control data could help.

Bias

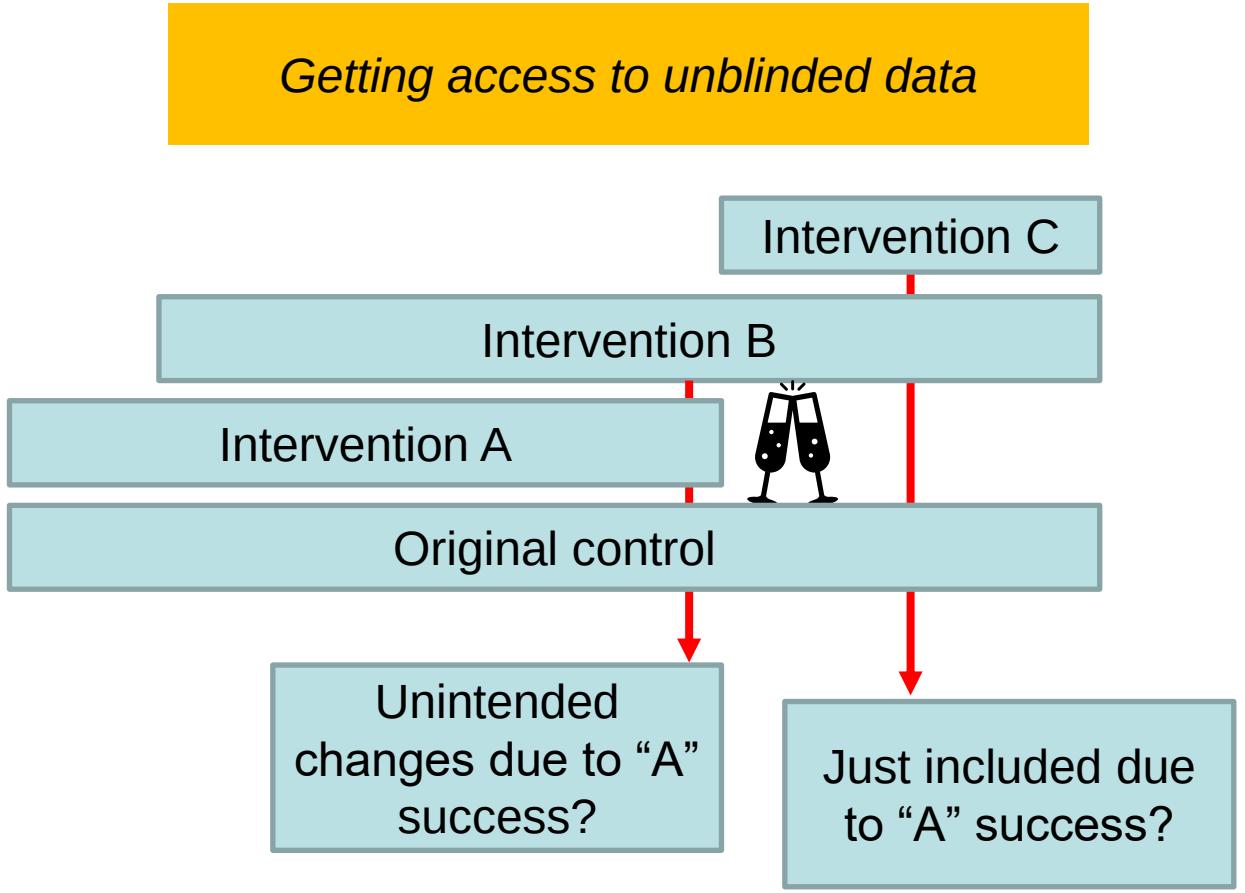
How to control which bias?

What is bias?

What is the definition of treatment effect?

What is the question of interest?

How to report subprotocol results while other arms are going on?



Discussion (Problem statement) – Concept paper

1. **Type I error control**
   - Clear guidance required on when which error rate control to be implemented
   - Could “Inferentially dependent” provide opportunity to for borrowing?

2. **Design characteristics that increase uncertainty in treatment effect estimates**
   - Guidance on when and how to use non-concurrent control data
   - How to “design” to increase confidence in non-concurrent control data?
   - How to change the control group?
   - Addition/removal of arms, changes to allocation ratios happen → Need to be addressed.

3. **Bias: How to control which bias?**
   - What is bias? → What is the treatment effect? → What is the question of interest?
   - How to report subprotocol results while other arms are going on?

Focus discussions on “when & how” instead of the “why not”