

# Multiplicity Adjustments in Multi-Armed Trials with Inferentially Independent Hypotheses

EMA MWP Interested Parties Meeting

Virtual, June 7th 2024

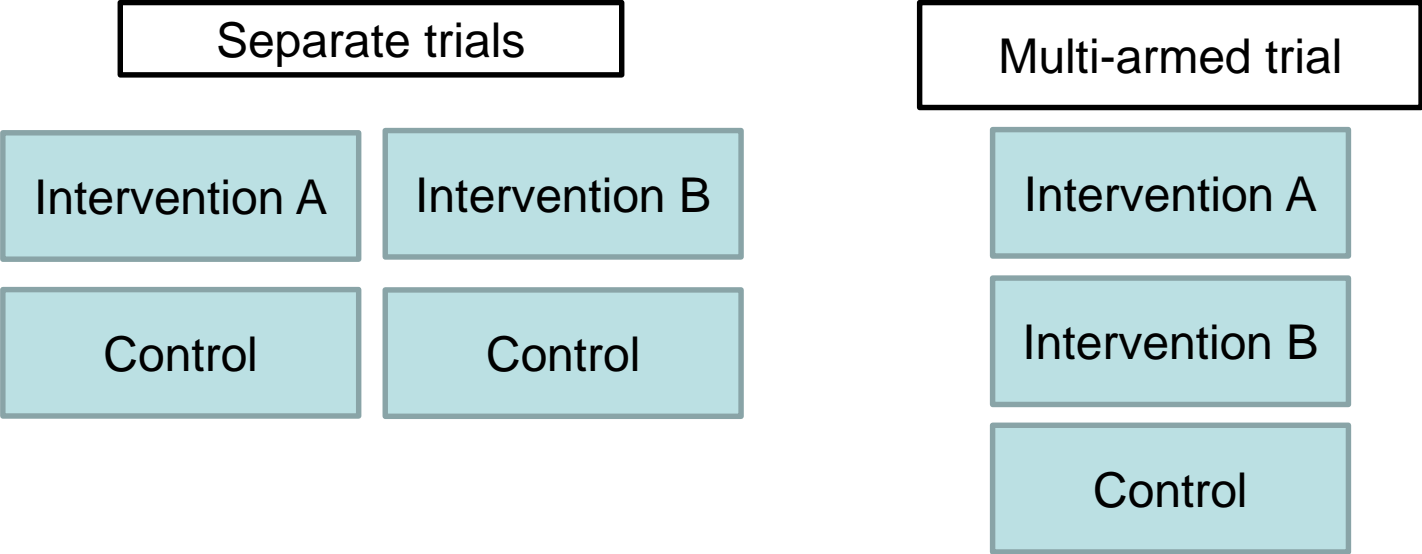
Tobias Mielke (J&J) – Acknowledging input of EFSPi colleagues

# Problem description

Multi-armed trials (incl. platform trials) are implemented to **efficiently** test multiple hypotheses of interest

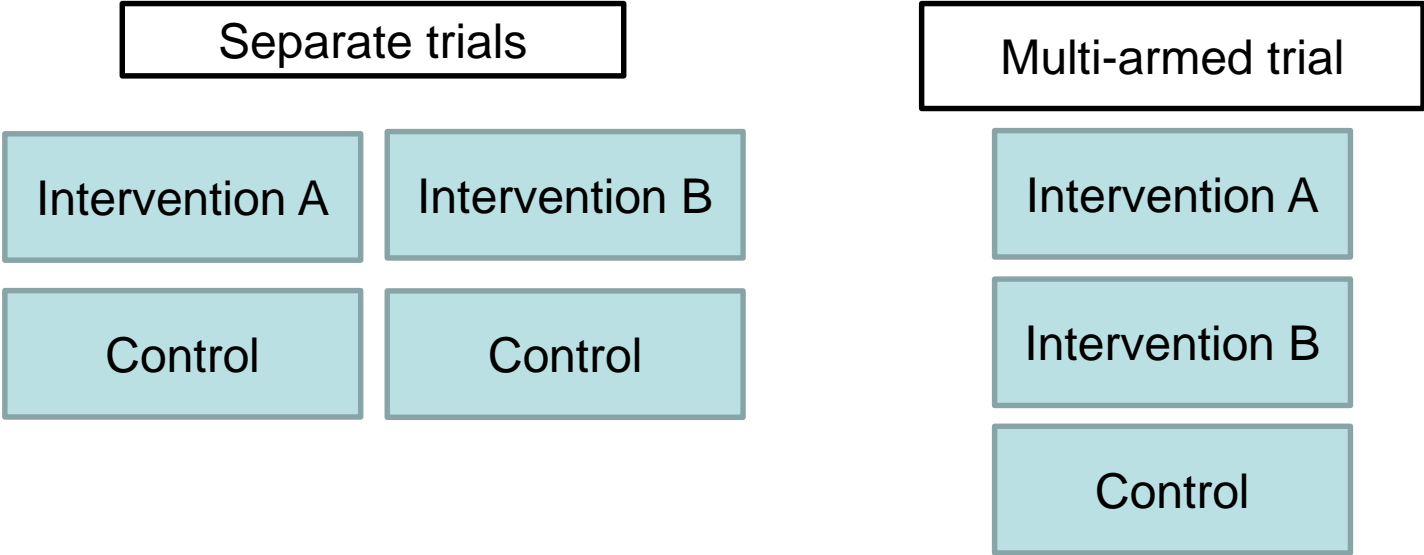
- Control of the FWER was required in the past, i.e. the probability of at least one type-1 error
- Recent publications and regulatory guidance (FDA) shifted this view, arguing that FWER would also not be controlled if hypotheses were tested in separate trials.
- Still, need for multiplicity control depends on the dependence of hypotheses (e.g. different doses of the same intervention)
- Common concern raised: chance on conducting multiple type-1 errors (k-FWER) may increase within multi-armed trials (e.g. through random low on control group).
- **Concern:** The k-FWER should not be a reason to stick to past practice of FWER control.

# Example Description: Hypotheses $\mu_A \leq \mu_C$ and $\mu_B \leq \mu_C$



Design	Allocation (vs. control)	At least one error	Two errors
Separate trials	1:1 and 1:1 (total 1:1:2)	4.94%	0.06%
Multi-armed non adjusted	1:1:1	4.53%	0.46%
Multi-armed Bonferroni-Holm	1:1:1	2.32%	0.39%

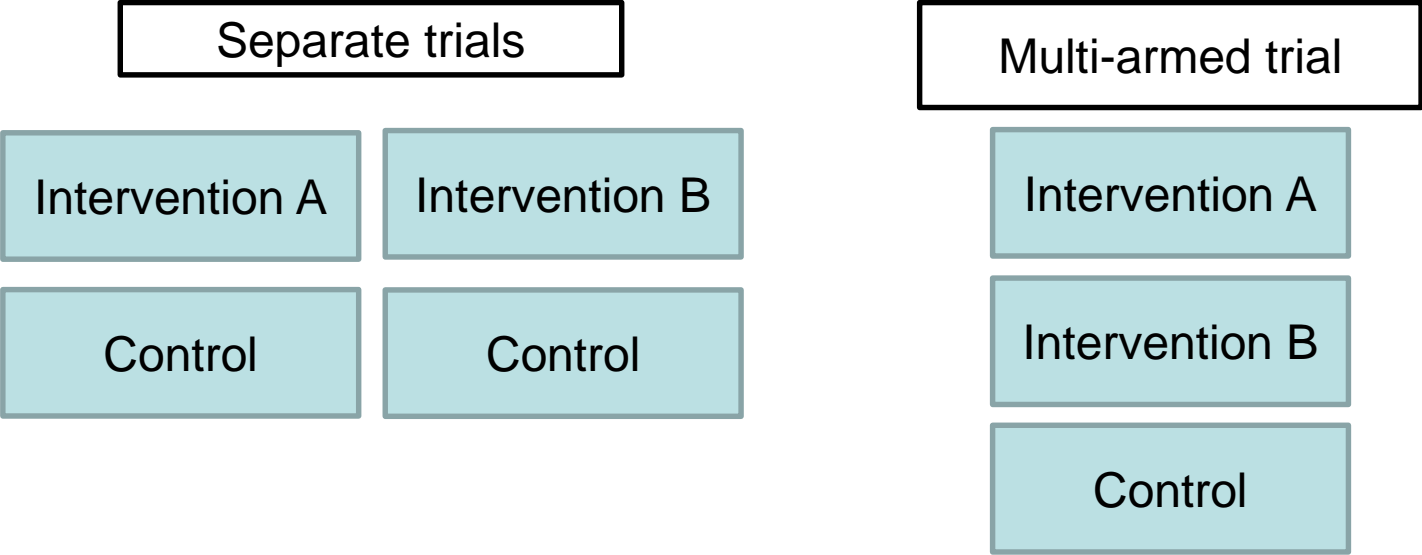
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Considered no issue

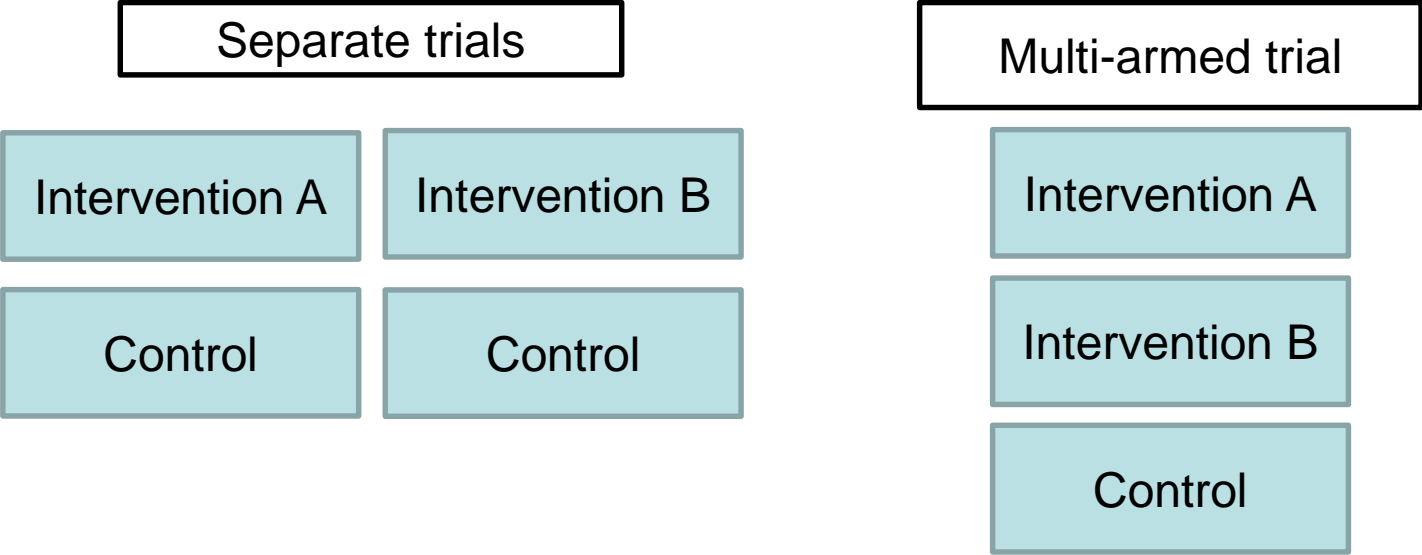
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Considered as issue

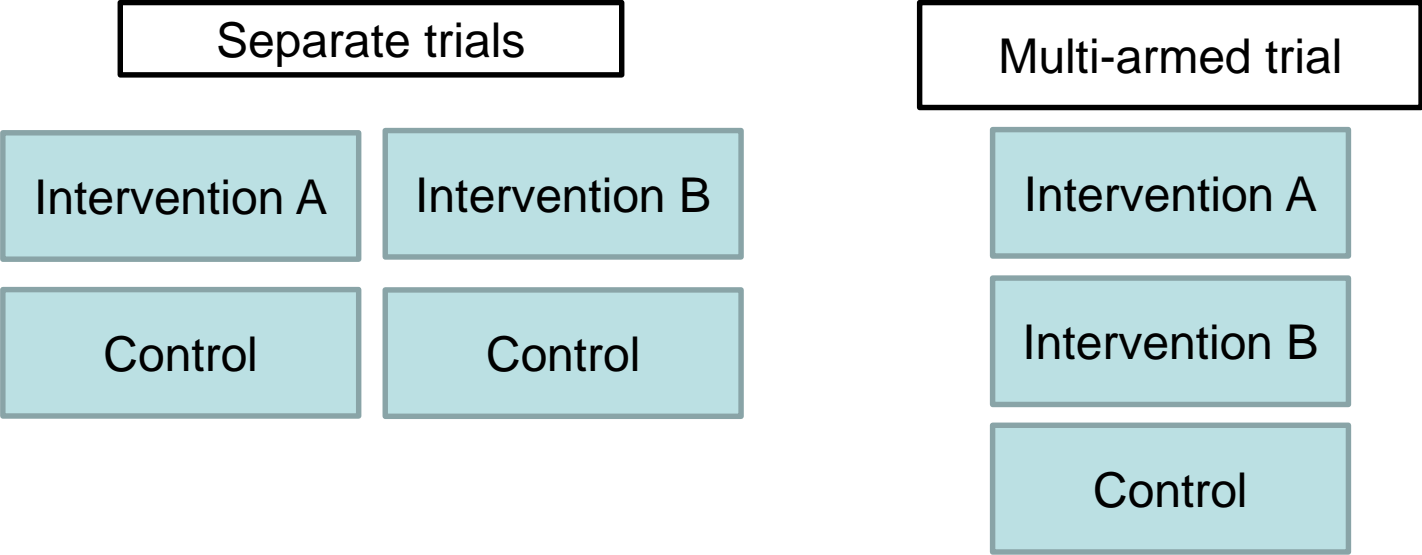
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If a) no need to control FWER and b) 2-FWER acceptable for Bonferroni-Holm, why would similar 2-FWER be considered as unacceptable for “unadjusted” testing?

# Guidance required

## Is there a need for **k-FWER** control?

If this is brought forward as reason to argue for multiplicity control:

- a) Why would **k-FWER** be an issue, if isn't for e.g. Bonferroni-Holm?
- b) What level of **k-FWER** would be considered as adequate?

## Definition of inferential independence

When are hypotheses considered as dependent?

- Does intervention owner matter?
- Does mechanism of action matter?
- How to prove independence of hypotheses?