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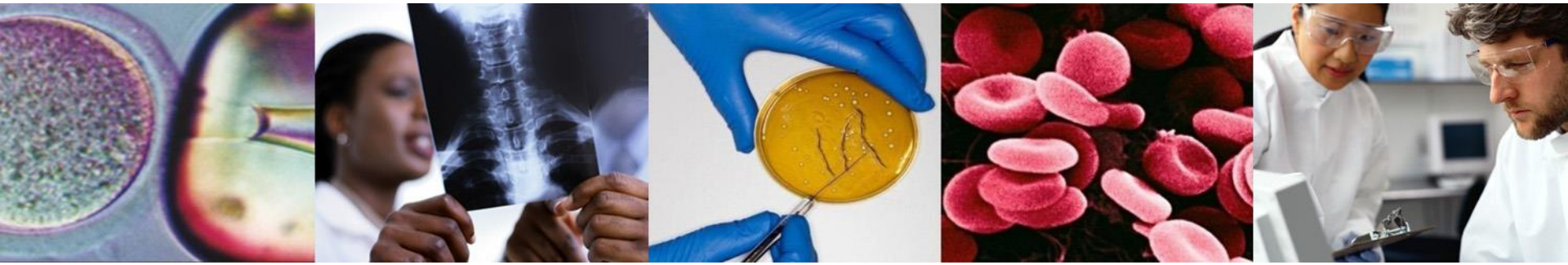

Adaptive Multi Arm designs for implementation laboratories

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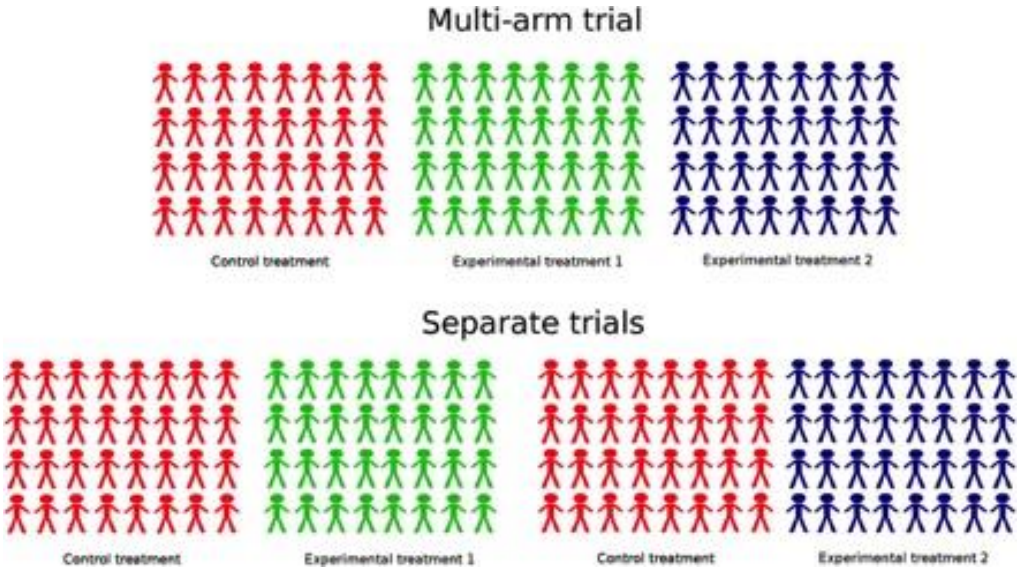
Novel study designs

- There is a strong need for more efficient and informative trial designs:
  - to make a correct decision about an intervention;
  - to increase the number of interventions evaluated given limited financial and patient resources;
  - to (as much as possible) ensure that patients on the trial are not subjected to harmful or non-effective interventions.

- I'll briefly review some examples of these designs.

Multi-arm trials

- Multi-arm trials provide big efficiency benefits over separate randomised trials due to a shared control group.



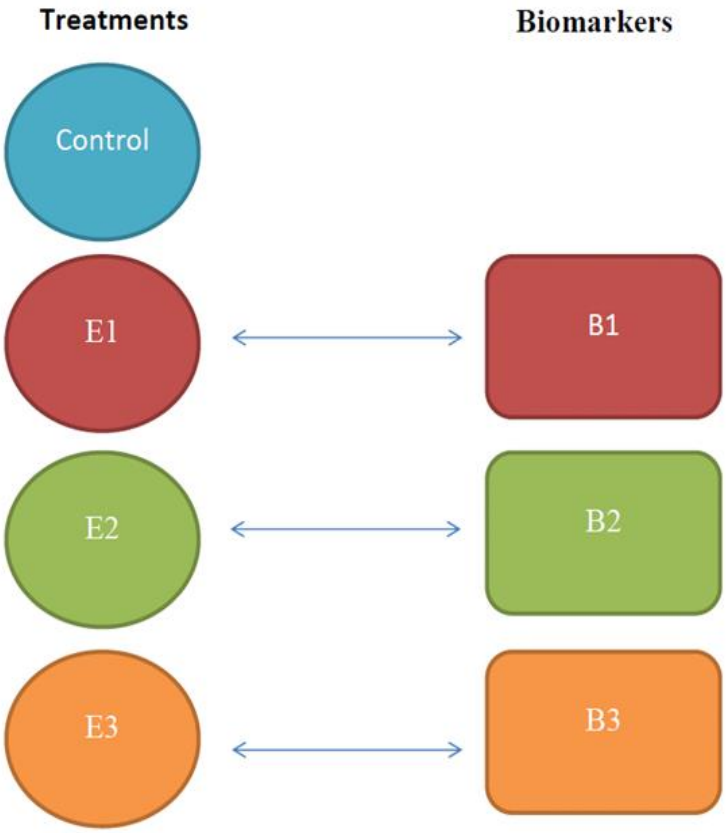
- Also lower administrative and logistical effort compared to separate trials.

Multi Arm Multi Stage (MAMS)

- Can also add interim analyses (multi-arm multi-stage).
- At the interim analyses, modifications can be made based on the results so far.
  - Ineffective interventions could be dropped;
  - The allocation to different interventions could be changed;
  - Trial could be stopped early if effective intervention found.
- Interim analyses generally add additional efficiency and make the trial more ethical (on average).

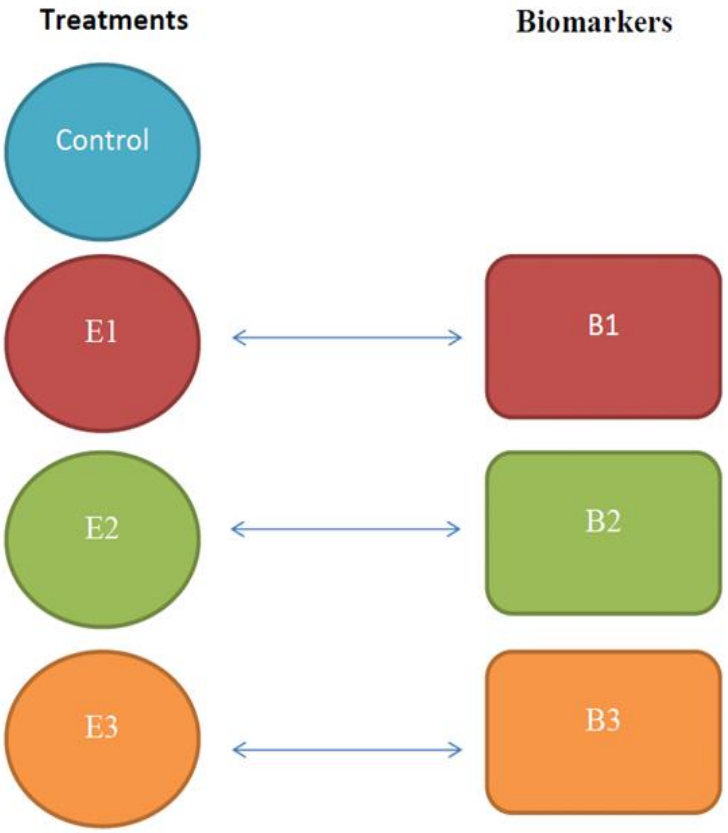
Umbrella studies

- When treatments may work differently in different patient groups, can use an *umbrella trial.*
- Logistical and statistical efficiency gains, similar to multi-arm trials.
- More patients can receive a treatment targeted at their biomarker profile.



Umbrella studies

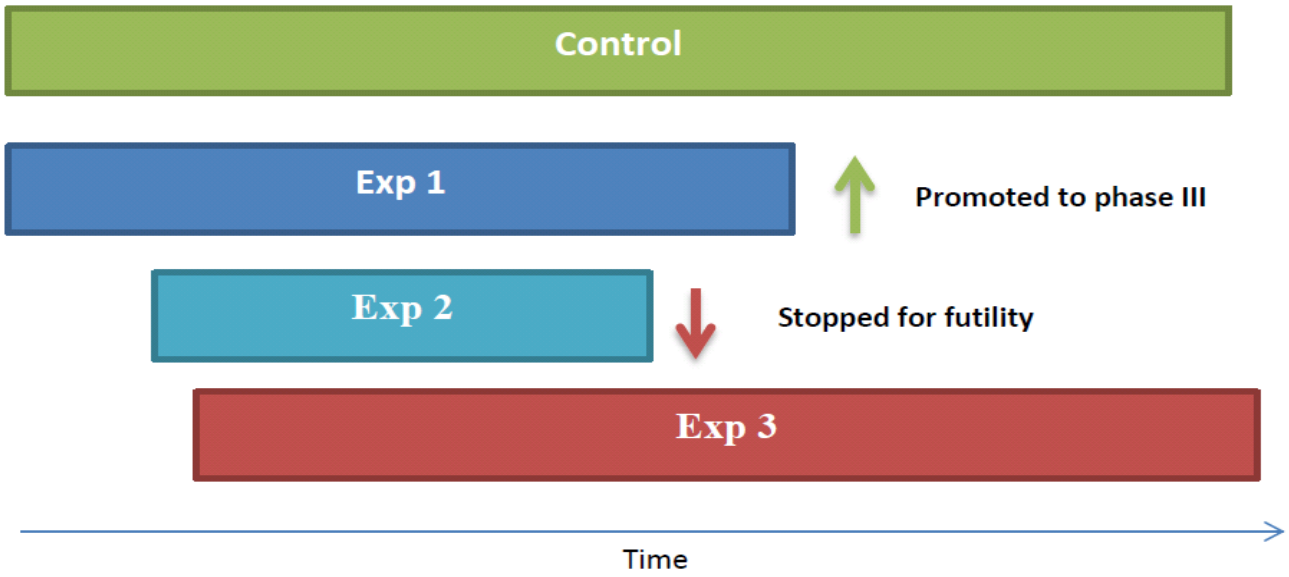
- By using an adaptive design, can guide allocation to different treatments using the subgroup information.
- This improves the power of detecting subgroup effects[1].



[1]Wason, J. M., Abraham, J. E., Baird, R. D., Gournaris, I., Vallier, A. L., Brenton, J. D., ... & Mander, A. P. (2015). A Bayesian adaptive design for biomarker trials with linked treatments. *British journal of cancer*, *113*(5), 699.

Platform trials

- Add new treatments/biomarkers as they become available.



- Allows efficient starting of testing new treatments.
- Especially useful when linked to a patient registry/cohort.

Applying novel designs to implementation laboratories

- These are primarily proposed in context of:
  - individually randomised;
  - parallel group;
  - drug trials.
- However could they provide advantages in implementation laboratories?
- Yes, I believe so, but some issues need to be considered.

Applying novel designs to implementation laboratories

- Potential benefits would be:
  - **MAMS**: Evaluation of more interventions with ineffective ones stopping early, and more focus on effective ones.
  - **Umbrella**: Consideration of how interventions may work differently in different types of centres/clusters.
  - **Platform**: introduction of new interventions during the evaluation in a statistically robust way.
- Let's examine some issues that may arise.

Clustering

- Clearly clustering is a characteristic of implementation laboratories.
- There is a limited but growing literature on adaptive designs when data is clustered: e.g. Lake et al.[1], Grayling et al.[2]
- Generally there are some issues when the number of clusters is **small;**
  - does not seem to be the case for implementation laboratories.

[1]Lake S, et al. Sample size re-estimation in cluster randomization trials. *Statistics in medicine* (2002)
2. Grayling M et al. Group-sequential designs for stepped-wedge cluster randomised trials. *Clinical Trials* (2017)

Routinely collected endpoints

- The use of routinely collected data is very efficient, but may cause issues in trials, e.g. missing data, informative observation times, lower data quality.

REVIEW Open Access

Routinely collected data for randomized trials: promises, barriers, and implications

Kimberly A. Mc Cord[1], Rustam Al-Shahi Salman[2], Shaun Treweek[3], Heidi Gardner[3], Daniel Strech[4], William Whiteley[2], John P. A. Ioannidis[5,6,7,8,9] and Lars G. Hemkens[1*]

- One could actually use an adaptive approach that allows changes if some measure of bias is higher than expected.

Routinely collected endpoints

- Likely that adaptive multi-arm designs could suffer more:
- Data collection affected by arm in some hard to model way - may cause spurious differences;
- For adaptive approaches to be successful, interims need to be done **quickly** and to a **high level of quality**: this might be difficult to do without substantial data management involvement.
- are routinely collected endpoints collected sufficiently **quickly** for adaptive approaches to provide utility?

Drift

- So called ‘drift’ in trials can be caused by:
  - Patient-drift: patient (or cluster) characteristics are different early in the trial and later.
  - Treatment-drift: change in effectiveness of control or standard of care over the course of the trial.
- Worth bearing in mind the likelihood and potential effect of this when designing adaptive trials.

Drift

- In individually randomised trials, using designs that don't change the allocation, with concurrent controls should minimise impact of drift.
- More complex designs are affected, but large drift needed.

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MAIN PAPER

WILEY

Response-adaptive designs for binary responses: How to offer patient benefit while being robust to time trends?

Sofía S. Villar[1] | Jack Bowden[2] | James Wason[1]

- Unclear for implementation laboratories though.

Summary

- Strong potential for novel trial designs to be useful in evaluating interventions in implementation laboratories.

- However there are a number of issues which need investigation to determine if increased bias or reduced efficiency is an issue.

- This prompts the need for additional methodology research in the area – perhaps today we can start this collaboration!