Innovative study designs for small populations

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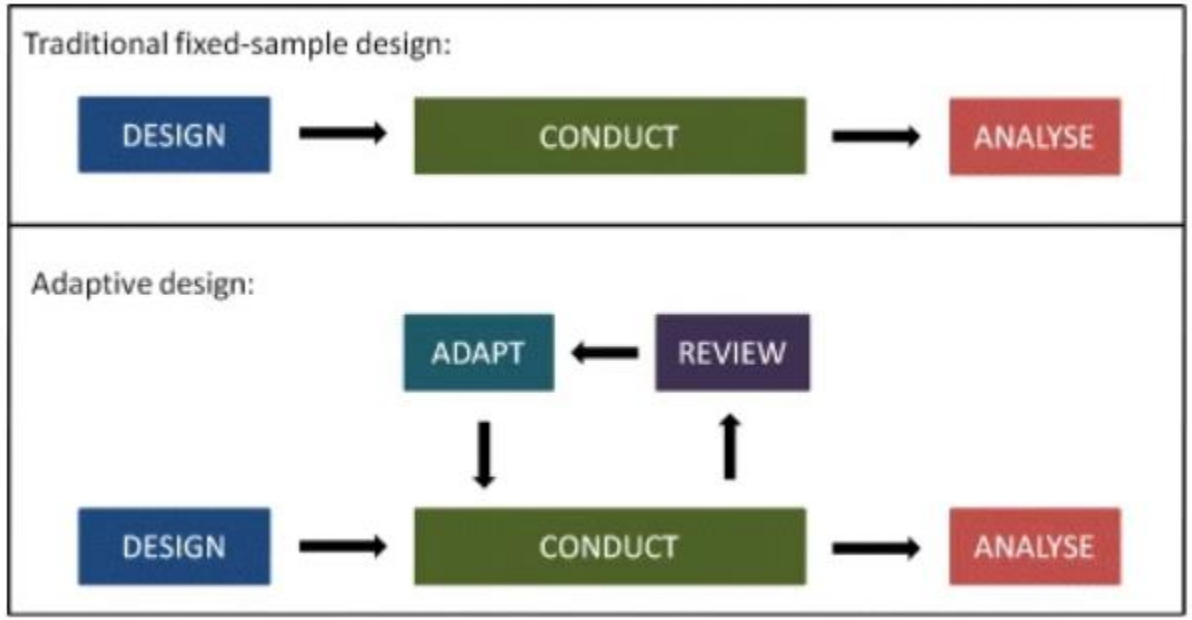
GUIDELINE ON CLINICAL TRIALS IN SMALL POPULATIONS

Background

Clinical trials in small populations present a number of innovative statistical approaches associated with the need to draw inference from small sample sizes. Innovative methodological approaches for study design such as Master Protocols (**Platform**, **Umbrella** and **Basket** trials) and **Adaptive** design play a crucial role in improving clinical trials and medicine assessment in small populations by ensuring the feasibility of the study and the validity of the results.

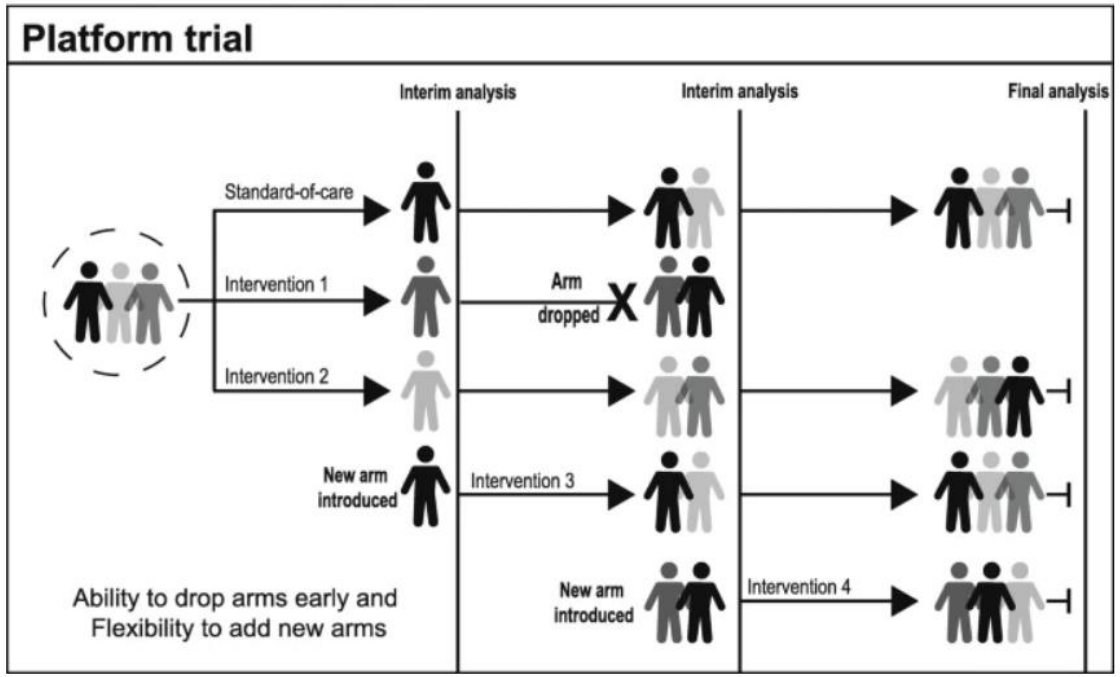
"**Master Protocol**" designs, are intended to answer multiple questions in one study.

Adaptive designs can make clinical trials more flexible by utilising results accumulating in the trial to modify the trial's course in accordance with pre-specified rules. Trials with an adaptive design are often more efficient, informative and ethical than trials with a traditional fixed design since they often make better use of resources such as time, and might require fewer participants.



Pallmann, P., Bedding, A.W., Choodari-Oskooei, B. *et al.* Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Med* **16**, 29 (2018). https://doi.org/10.1186/s12916-018-1017-7

Platform trials referred to as Multi-Arm, Multi-Stage (MAMS) design to evaluate several interventions against a common control group. These designs help to further accept additions or exclusions of new therapies or patient populations during the clinical trial. In a platform trial, interim analyses evaluate the efficacy or futility of each targeted therapy and use their results to add new ones or exclude certain study therapies.

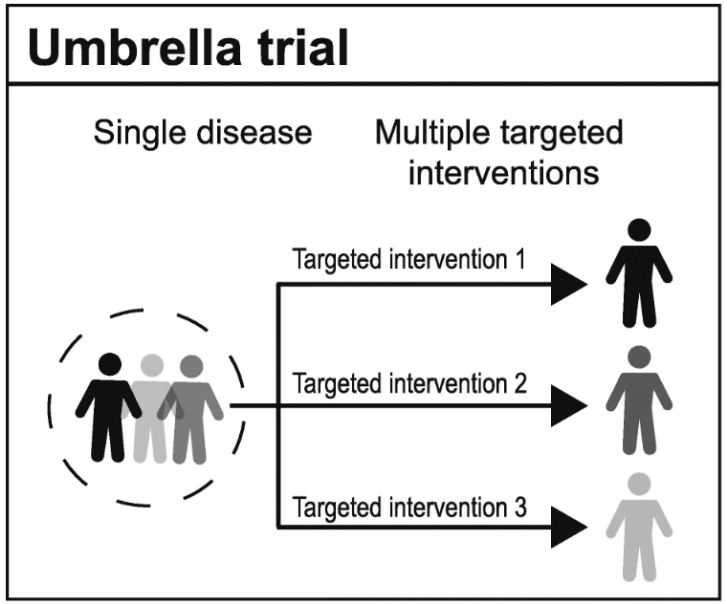


Park, J.J.H., Siden, E., Zoratti, M.J. *et al.* Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. *Trials* **20**, 572 (2019). https://doi.org/10.1186/s13063-019-3664-1

Umbrella trials are one class of master protocol design that evaluates multiple targeted therapies in a single disease setting. Conceptually, an umbrella design is simply a set of (sub)trials run in parallel.

It offers a selection of appealing advantages, including:

- that several treatment-related questions can be answered in a single trial;
- a potential reduction in the number of patients required (for instance, by including a common control arm).



Front Med (Lausanne). 2022; 9: 1037439.
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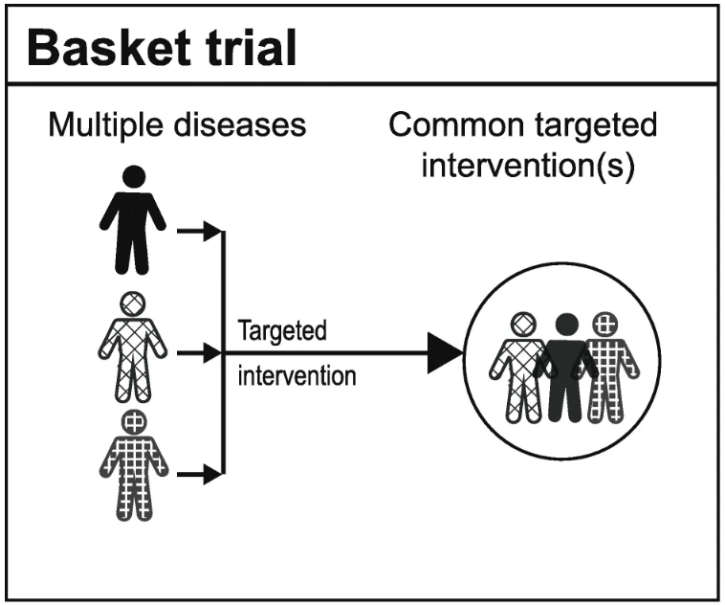
Basket trials refer to clinical trials conducted to test one treatment on multiple diseases that share common molecular alternations or other predictive risk factors. The US FDA considers a basket study to be adequate evidence for approval and recommends researchers utilize such trial designs.

A basket design makes the most sense when there is clinical reason that all the indications can be improved by the same molecular drug mechanism.



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Innovative Study Design Advantages

- Increase of Efficiency
- Improve of Ethical Standards
- Enhance of Data Quality and Reliability
- Personalized Medicine
- Optimization of Resources
- Patient-Centric Approaches
- Safety Monitoring

Critical challenge faced

Although the fundaments of these innovative approaches have been already streamlined in comprehensive scientific and regulatory guidelines and accepted at the regulatory level long ago, their implementation in clinical research practice remains very limited.

Reasons for limited application

- ***Conservatism and Resistance to Change*** **-->** Scientific and medical communities tend to be conservative and often prefer traditional and well-established methodologies. New approaches can appear risky or insufficiently validated compared to traditional methods.

- ***Complexity*** **-->** Innovative study designs can be complex to plan and manage. They require personnel with specific expertise in advanced methodologies and statistical analysis.

- ***Regulatory Concerns*** **-->** Even though regulatory authorities accept these approaches, there are often concerns regarding the interpretation of results, reproducibility, and generalizability of data collected using non-traditional methods.

- ***Lack of Familiarity*** **-->** Many researchers and clinicians may not be familiar with the new approaches and may lack the necessary training to implement them correctly.

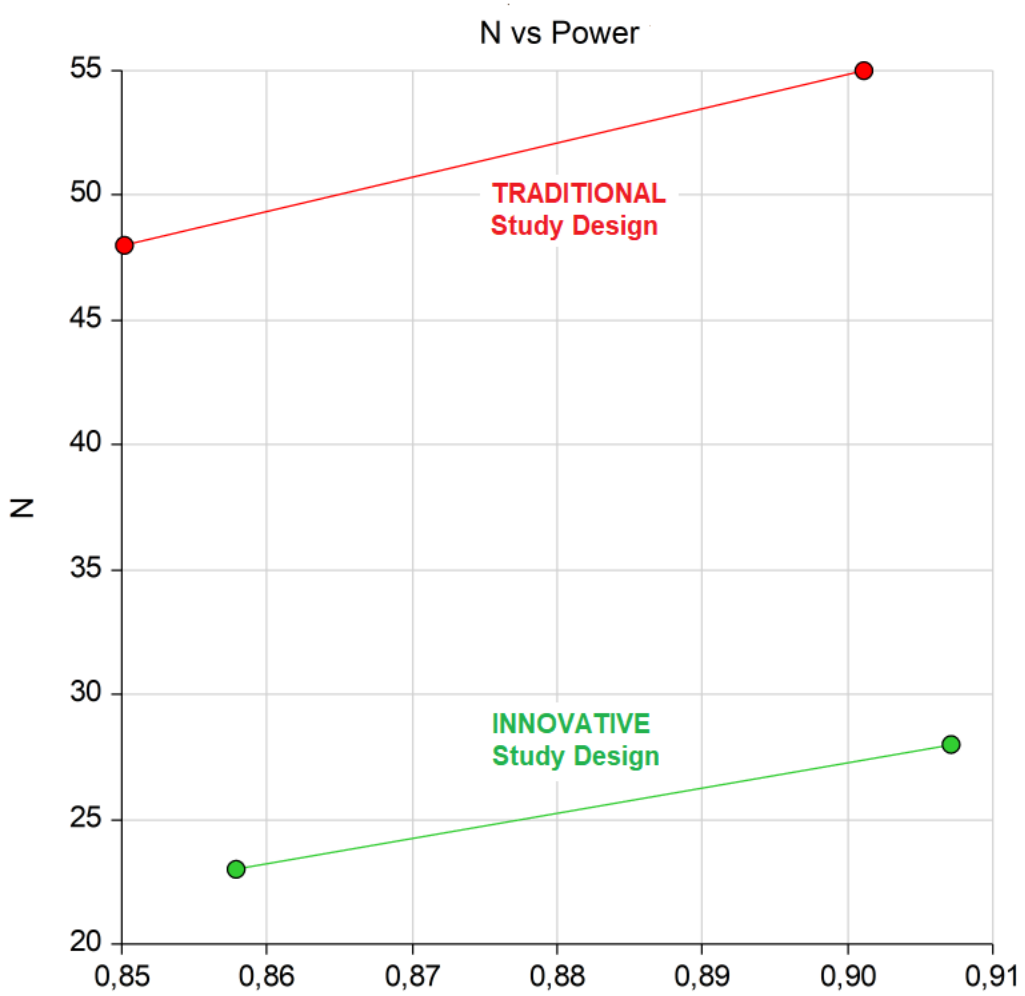
- ***Costs and Funding*** **-->** Innovative studies can require higher funding, and funders may be reluctant to invest in unconventional methodologies without a solid track record.

Proposal of possible intervention

Knowledge Transfer of Innovative Study Designs

Promoting Engagement of Medical and Research Professionals

- Regular organization of **Workshops and Seminars** to share insights about innovative study design.
- Incorporation of them in modules in **Continuing Medical Education (CME**) programs.
- Distributing **Publications and Case Studies** to highlight their successful implementation and effects.



Thank you

CVBF
Clinical Validation from Biopharmaceutical Findings

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NETWORK