Novel trial designs: Master protocol trials

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Abstract Conventional trial designs are resource and time-intensive. To accelerate the process of testing new interventions, we now have several novel research trial designs. This article focuses on master protocol trials, which allow several therapies to be tested within a single larger trial.

Keywords: Adaptive clinical trials as topic, clinical trials, research design

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INTRODUCTION

In previous articles in this series, we have discussed various research study designs, including the phases of clinical trials.[1-6] Conventionally, the development of a new intervention has followed a process of various sequential phases of the trial, with the phase 3 randomized controlled trial (RCT) considered the gold standard for establishing the efficacy of an intervention. RCTs offer several advantages, such as the ability to control for confounding and bias. However, the conventional trial process is very long, often taking several years between the initial phase of testing and marketing. Since these trials have predefined populations, interventions, and outcomes, it is not possible to adapt them to emerging information, and often, the long duration of the trial makes the results redundant. The lack of flexibility in the design of RCTs also limits the scope of research questions that can be addressed. RCTs are resource-intensive, need large samples, and are wasteful if the early phase testing is unsuccessful.

Various newer trial designs have been developed to overcome these challenges and increase the efficiency of trial conduct. Fundamentally, these designs allow adding preplanned flexibility to the trials through provisions such as parallel evaluation of multiple hypotheses and interventions, the addition of new intervention(s) during the trial, dropping of ineffective intervention(s), adaptive randomization to shift allocation ratio toward more promising treatment(s), seamless phasing of trials, among others.[7,8] Whereas many of these novel designs were initially implemented in oncology to address the need to target specific mutations or biomarkers, they are now prevalent in several other areas of biomedical research. Among these novel designs, this article focuses on master protocols.

MASTER PROTOCOLS

Master protocols test several research ideas within the overarching structure of a single trial. The sub-studies within the master protocol share common elements of

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design, infrastructure, and operations, making them more efficient and cost-effective. The three main types of master protocols include umbrella trials, basket trials, and platform trials.

UMBRELLA TRIALS

Umbrella trials typically test multiple targeted interventions for a single disease, with patients often being allocated to different arms depending on specific patient characteristics such as pathological (tumor subtype) or molecular (genetic) criteria. Umbrella trials could include different drugs but also multiple doses of the same drug in different arms as part of a dose-finding strategy. Additional interventions may be added as the trial progresses. Each sub-study could be a single arm or randomized, and if randomized, the control arm is often common for all the interventions being tested, thus increasing the chances of being allotted to an intervention. The interventions that show a signal for efficacy are considered for further testing. Figure 1 is a schematic diagram of an umbrella trial. Some of the challenges of umbrella trials include dealing with participants who could be randomized to multiple arms (e.g., being positive for multiple biomarkers) and determining the appropriate methods of randomization and analysis.

The HUDSON study was a phase 2 umbrella trial in patients with advanced lung cancer who had failed first-line therapy. Patients underwent molecular profiling of their tumors and were grouped based on the presence or absence of targetable mutations.[9] Group 1 was a biomarker-matched cohort where participants were subjected to one of 3 interventions, depending on the biomarker. Group 2 was a biomarker nonmatched cohort that received a different intervention (usually the accepted standard of care). The study allowed the investigators to examine the effect of 4 different interventions for one disease under one common umbrella.

BASKET TRIALS

Basket trials include participants with several different diseases with a common targetable lesion, who are treated with a common intervention. Basket studies are often single-arm studies; if a control (and randomization) is planned, it differs for each tumor type, depending on the standard of care. Additional disease types may be added as the trial progresses. Specific disease populations that show early evidence of response are considered for further testing. Figure 2 is a schematic diagram of a basket trial.

The DART trial is a single-arm basket trial looking at the effect of immunotherapy in patients with any one of 53 types of rare tumors.[10] The intervention is standardized across tumor types. Considering that many of the individual tumors are very rare, with reported incidences as low as 6 in 100,000, the basket design allows an efficient method to study the effect of interventions.

PLATFORM TRIALS (MULTI-ARM MULTI-STAGE TRIALS)

Platform trials are similar to umbrella trials in that they study multiple interventions for a single disease. However, unlike umbrella trials, platform trials use data that is collected to periodically re-design the trial and add or discontinue treatment arms, change the control arm, and determine which interventions will be carried forward to the next phase of testing. Platform trials also allow non-responders on a trial arm to be shifted to another intervention. This means that participants are no longer assigned to receive a treatment that is potentially ineffective. Figure 3 is a schematic representation of a platform trial.

The STAMPEDE: Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy was one of the earliest MAMS trials investigating therapies for patients with advanced prostate cancer.

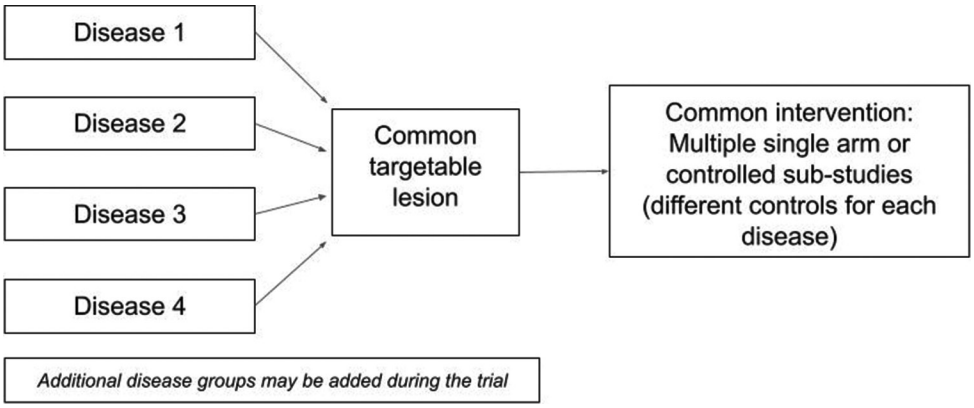

Figure 1: Schematic representation of a basket trial

Between 2005 and 2023, the trial used one control arm and tested 10 different interventions.[11] Based on early phase results, therapies which showed proof of efficacy were carried into the next phase of testing, whereas those which were ineffective were dropped. During the COVID-19 pandemic, the RECOVERY (Randomized Evaluation of COVID-19 Therapy) trial allowed the rapid identification of effective (and ineffective) therapies using a MAMS design.[12] The STAMPEDE trial used the technique proposed by Royston and colleagues to identify and eliminate inferior therapies at an early stage.[13] This method uses hazards of an intermediate time-to-event outcome measure to select therapies which should be continued to be tested on a final time-to-event outcome measure.

Bayesian decision rules are also sometimes used to determine the time of discontinuity of therapies showing lower chances of success. The method involves the calculation of Bayesian predictive probabilities of a therapy being successful in the future course of the trial at each point of interim analysis. A therapy may be discontinued from the trial when its probability of success drops sufficiently low, say below a predetermined value.[14] In addition, these probabilities can also be used in adapting the randomization rule at each interim point to ensure a proportionately higher allocation of participants to therapies with better chances of success. Table 1 summarizes the key features of the three types of master trials

CONCLUSION

Compared to conventional trial designs, master protocols offer several benefits: they are resource-effective, answer multiple questions in a relatively short period, are feasible

Table 1: Types of master protocol trials

	Umbrella trial	Basket trial	Platform trial
Disease type	Single	Multiple	Single
Target	Multiple	Single	Different biological mechanisms
Therapies	Multiple	Single	Multiple
Control (if used)	Could be shared across groups	Multiple, depending on disease	Usually single - can be adapted depending on emerging information
Multi-stage	Not usually	Not usually	Yes

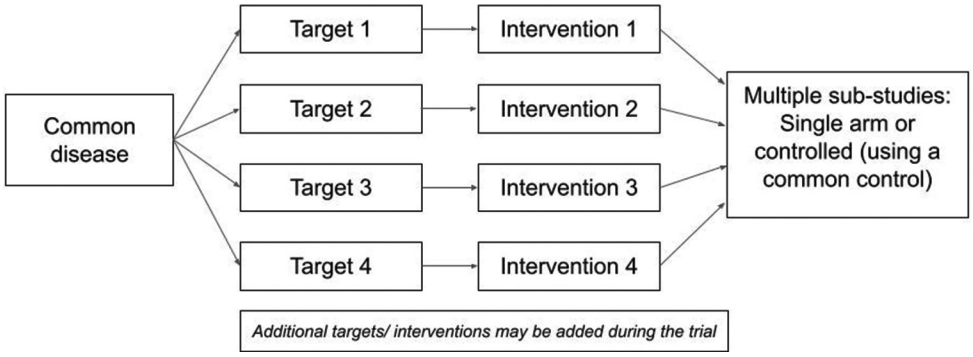

Figure 2: Schematic representation of an umbrella trial

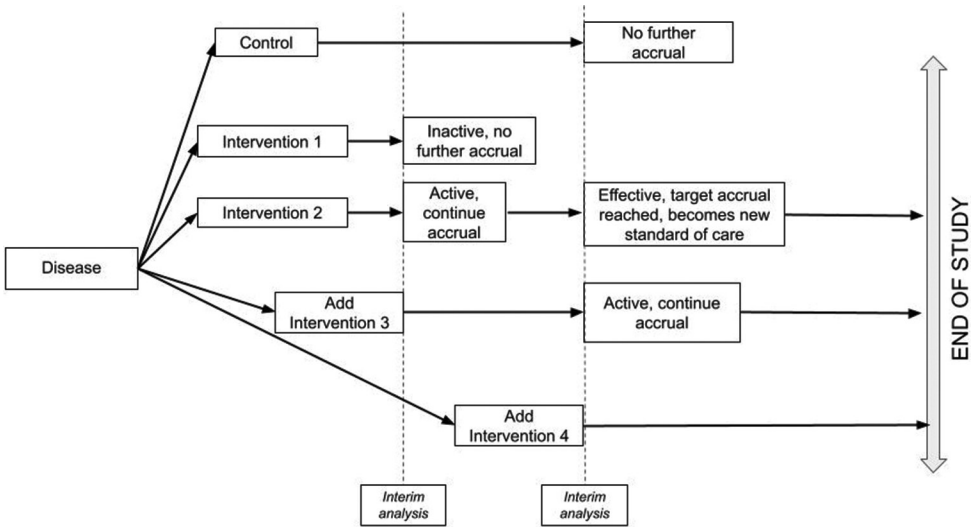

Figure 3: Schematic representation of a platform trial

in rare populations, and utilize emerging data to inform the trial, thus retaining the focus on potentially effective interventions. There has been an exponential increase in the number of master protocol trials in the last decade. However, these trials have complex designs, need advanced statistical inputs, need careful design and analysis to deal with the multiple looks at the data and retain the integrity of the trial, and need careful interpretation.

Suggested reading

Park JJH, Detry MA, Murthy S, Guyatt G, Mills EJ. How to Use and Interpret the Results of a Platform Trial: Users' Guide to the Medical Literature. JAMA. 2022;327:67-74.

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Conflicts of interest

There are no conflicts of interest.

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