

INNOVATIVE TRIALS

HOW WE SUPPORT ADAPTIVE TRIAL DESIGN

CURRENT SITUATION

Conventional randomized clinical trials (RCTs) typically follow a parallel-group setup where the randomization process is performed only once per patient throughout the study. However, with the complete sequencing of the Human Genome in 2003, the field of medicine and pharmaceutical sciences underwent significant transformations in their relentless pursuit of combating complex diseases.

With the advent of this new era of precision medicine, the field of oncology has benefited considerably from the identification of unique molecular features that drive malignancies. Based on this, future clinical investigations are allowing for individualized, targeted treatments promising a successful transformation of the outlook for several fatal cancers.

A key pillar in conducting this kind of new clinical research is using innovative clinical trial designs like adaptive platform trials (APTs) in which randomization and even multiple randomization of patients over various phases is an integral part.

LANDSCAPE OF TRIAL DESIGNS

A basket trial, an umbrella trial, and a platform trial are all innovative types of clinical trial designs that aim to streamline and optimize the drug development process. The common thread among these trial designs is their flexibility and ability to make modifications based on accumulating data during the trial. Here's how adaptive trials can be incorporated into each of these designs. While basket trials typically possess minimal adaptive characteristics, adaptability progressively increases towards umbrella trials and becomes an essential component in platform trials.

Basket Trial: is a type of clinical trial design that evaluates the effectiveness of a particular treatment across multiple diseases or conditions that share a common molecular alteration or genetic mutation. In other words, patients with different types of cancer or multiple diseases are grouped together based on a specific genetic alteration, and they receive the same targeted therapy or intervention. This approach allows researchers to assess whether the treatment has efficacy across various diseases with the same genetic target.

Umbrella Trial: is a trial design that involves simultaneously evaluating multiple targeted therapies or interventions in a single disease or condition. Patients with a specific disease or condition are enrolled in the trial, and they can be assigned to different treatment arms in an iterative manner based on specific biomarkers or molecular characteristics. This design enables the evaluation of multiple treatments and facilitates the identification of personalized therapies based on individual patient characteristics.

Platform Trial: is a type of clinical trial design that enables the continuous evaluation of multiple interventions across multiple diseases or conditions. It is an adaptive trial design that allows for the addition and removal of different treatments or interventions as the trial progresses. Patients with different diseases or conditions are enrolled, and they may be assigned to different interventions based on predefined criteria or adaptive randomization. This design allows for more efficient testing of multiple interventions, reduces the time and cost of drug development, and facilitates the identification of effective treatments across various diseases.

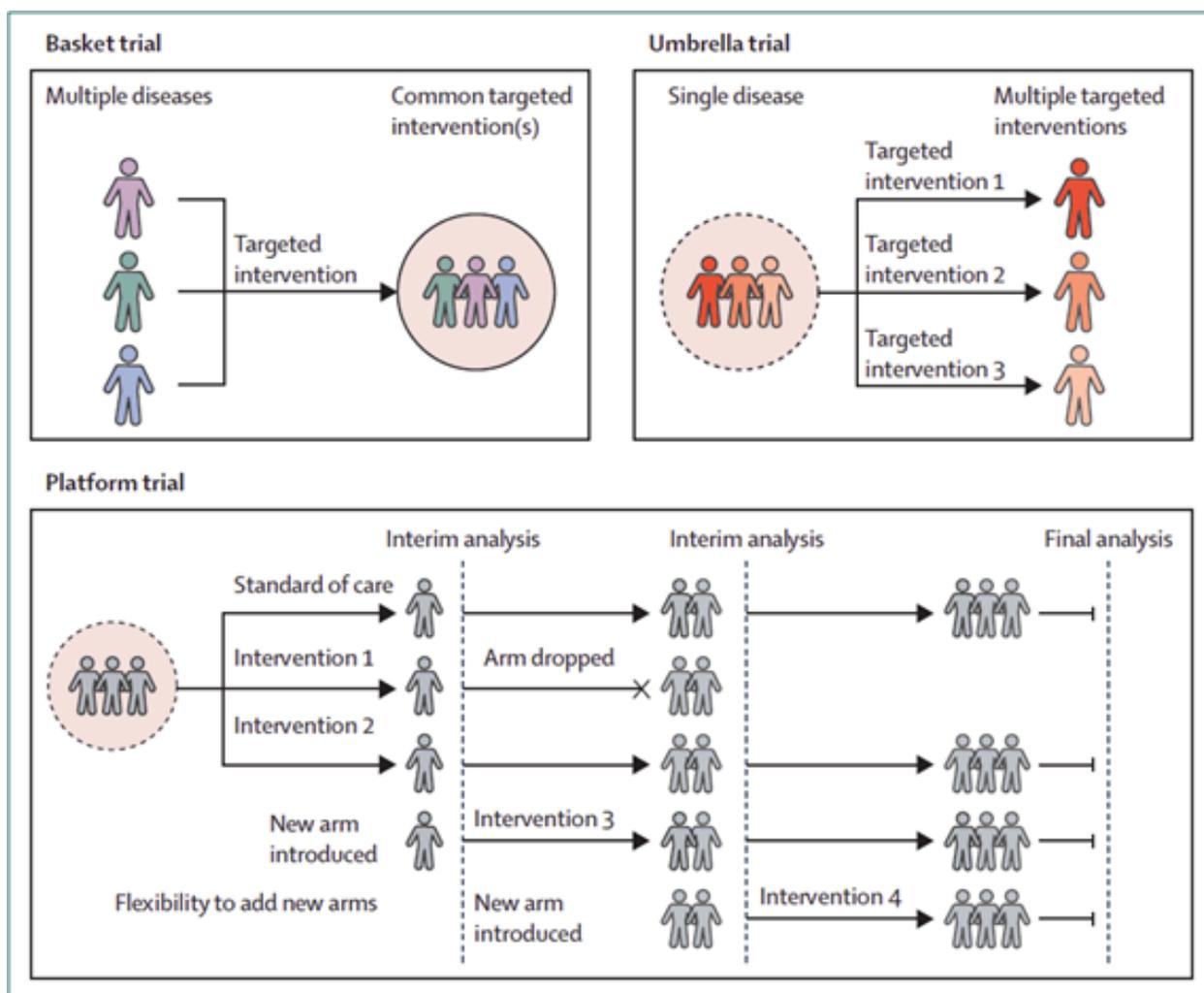


Figure 1. Source: Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols
<https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3664-1>

WHAT IS AN ADAPTIVE TRIAL?

An adaptive trial, also known as an adaptive design trial, is a type of clinical trial that allows for prospectively planned modifications to the trial design or conduct based on interim data analysis. It involves making adaptations or modifications during the course of the trial while maintaining the scientific integrity and validity of the study.

In a traditional clinical trial, the trial design is fixed from the beginning, and any modifications are typically considered only after the trial is completed. In contrast, an adaptive trial allows for modifications based on accumulating data while the trial is ongoing. This flexibility can lead to more efficient and informative trials, as adaptations can be made to optimize patient allocation, treatment regimens, sample sizes, or study endpoints based on emerging data.

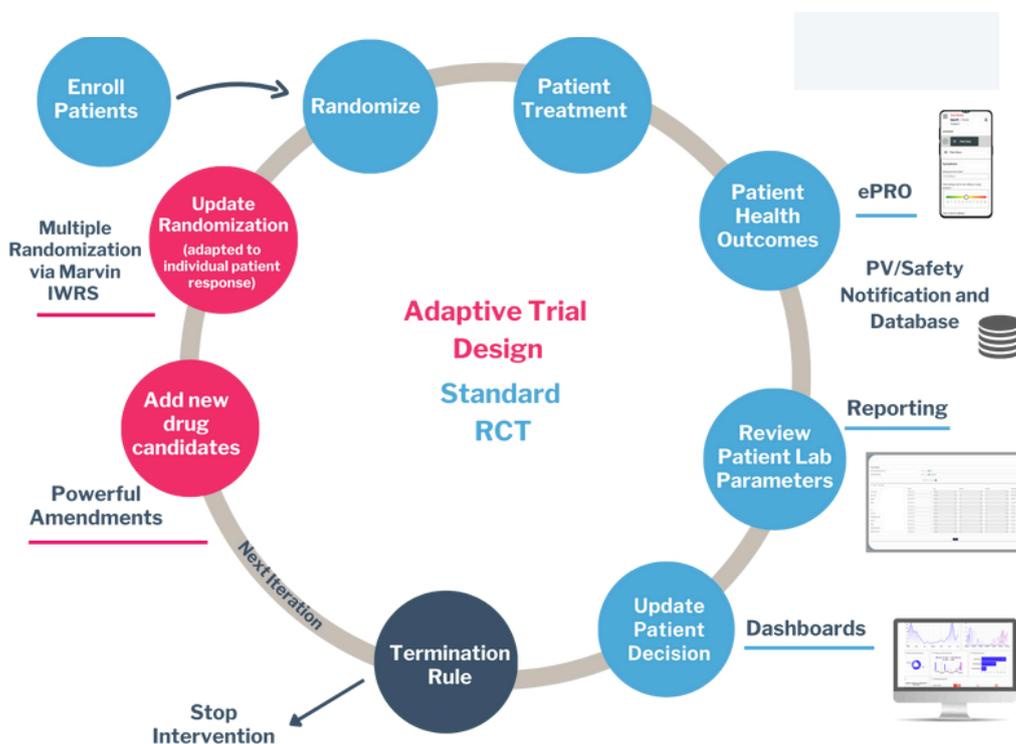


Figure 2. APT Randomization requirements, operational flow
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Adaptive trials are particularly useful in situations where there is uncertainty about the optimal treatment regimen, patient population, or dose selection. By enabling modifications based on interim data analysis, adaptive trials can increase the likelihood of identifying effective treatments, reduce the required number of patients, enhance overall trial efficiency, and significantly reduce time to actual drug licensing from **12 years to 5 years**.*

*Fountzilias, E., Tsimberidou, A.M., Vo, H.H. et al. Clinical trial design in the era of precision medicine. *Genome Med* 14, 101 (2022). <https://doi.org/10.1186/s13073-022-01102-1>

It's important to note that adaptive trials require careful planning, statistical expertise, and regulatory considerations to ensure the integrity and validity of the study. The adaptations must be pre-specified in a detailed statistical analysis plan to maintain scientific rigor and avoid potential biases.

CHALLENGES

To conduct an adaptive trial smoothly, it is essential to consider and address the challenges that may arise during its implementation, and they are as follow:

- **Trial transparency and integrity:** As various adaptations are made during the course of an adaptive trial, maintaining trial integrity and transparency becomes crucial.
- **Statistical complexity:** Due to its nature to evaluate multiple interventions, adaptive trials often involve more complex statistical methodologies compared to traditional fixed-design trials.
- **Resource implications:** Adaptive trials can be resource intensive. The need for more frequent data monitoring, analyses, and adaptations may require additional time, funding, and expertise.
- **Decision-making and operational considerations:** Adaptive trials require frequent decision-making based on interim data analysis.
- **Regulatory considerations:** Regulatory agencies play a crucial role in the approval and oversight of clinical trials.
- **Ethical implications:** Adaptive trials raise ethical considerations related to patient safety and informed consent.

HOW WE CAN HELP ADDRESSING THESE CHALLENGES

Our solution helps to address the increasingly dawning innovative clinical trial designs. It supports both, algorithm-based as well as **block-wise randomization** methods. These basic randomization methods could even be configured in a way to seamlessly switch at a defined stage of the study (e.g. after recruitment of 5 or 10 patients).

The available algorithm-based randomization method spans from conventional **variance minimization algorithms**, where participants are randomly assigned to different study arms with equal probability, to **more complex algorithms** that can be adapted throughout study duration.

These more complex algorithms are enabled by Marvin's **covariate-adjusted** response-adaptive (CARA) randomization method allowing the set-up of requirements in adaptive randomized platform trials. CARA can account for:

- **covariates**, e.g. identified dedicated score levels per patient at baseline, to achieve a targeted distribution ratio across arms per covariate level or category.
- **response rates**, as result of interim analyses, to ensure that more promising therapies will be assigned with a higher probability during the course of the study.

All of the randomization methods listed above can additionally factor-in multiple stratification factors to target certain distribution ratios per stratum.

Finally, in 2021, we introduced the capability to allow for an iterative (multiple) randomization of one patient in one study. The available treatment arms may include several arms or interventions throughout one study and the arms can be adjusted over time by introducing new arms as well as the dropping of arms. Following dedicated features support the flexibility to adapt the randomization process as needed throughout the research project:

Algorithm-based Randomization: Participants are randomly assigned to different study arms with equal probability.

Block-wise Randomization: Participants are randomized in blocks to ensure balance between treatment groups at specific intervals.

Stratified Randomization: Participants are first grouped into strata based on specific criteria (e.g., age, gender, severity of the condition) and then randomized within each stratum.

Adaptive Randomization: This algorithm allows for modification of the randomization ratio during the study based on accumulating data. It is commonly used in adaptive clinical trials, where the allocation to different treatment arms can be adjusted based on interim analyses or predefined criteria.

Based on this **powerful IWRS**, Marvin comes together with a highly flexible reporting tool to reveal early evidence for efficacy of treatment arms prior, during, and after interim analyses. Relevant eCRF details like e.g., a patient's minimal residual disease (MRD) test results and lab parameters can be delivered quickly to review committees via the EvidentIQ Safety Notification tool to address the crucial trial transparency and to achieve regulatory approval in a timely manner. This **E2B mailer is EDC agnostic** and integrates with other systems, allowing for a smooth and hassle-free experience during the study.

(<https://news.evidentiq.com/b2b-safety-notifications>)

The eCRF in our eClinical solution can be set-up in an **SDTM-compliant fashion** to generate submission data much faster for the FDA.

CONCLUSION

In summary, adaptive trials offer a transformative approach to clinical research, driven by **patient-centered precision medicine**. Overcoming the associated challenges requires careful planning, collaboration, eCRF set-up and expertise in adaptive trial design. Regulatory agencies, researchers, and statisticians are working together to develop guidelines and frameworks for effective implementation.

The need for more frequent data monitoring and adaptations may require additional resources and specialized personnel. Adaptive trials, well-suited for testing multiple interventions in various diseases, support continuous quality improvement and expedite the identification of comparative treatment effectiveness. Embracing adaptive trials has the potential to **revolutionize therapy development and enhance patient outcomes**.

ABOUT US

We are proud of our role in providing cutting-edge technology to bring vital medications to the market. Our dedication to excellence and innovation drives us to make a meaningful impact on healthcare delivery, improving the lives of patients worldwide.



Every day saved can make a difference.



AB-Cube Germany GmbH, (formerly XClinical), is a leading European provider of eClinical technologies and the developer of the Marvin EDC platform. Marvin offers an integrated suite of clinical modules, including EDC, IWRS/RTSM, Medical Coding, ePRO, and advanced reporting tools, designed to support complex and oncology-focused clinical trials. With more than two decades of experience and a strong commitment to data quality, compliance, and innovation, AB-Cube Germany empowers sponsors, CROs, academic and research institutions worldwide to conduct efficient, high-integrity clinical studies.

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