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# Novel Approaches to Clinical Trial Design and Implementation

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## ABSTRACT

Companies are working hard to adopt and execute efficient and innovative approaches to accelerate drug releases, giving the clinical research sector a big makeover. The difficulty of powering and recruiting participants into a study in a small and frequently heterogeneous population, the dearth of natural history data informing crucial design elements, and the ethical and recruitment difficulties associated with assigning patients to a placebo arm are all obstacles to the clinical development of new therapies. The goal of this article is to present innovative clinical trial design methods, including adaptive designs, Bayesian techniques, and master protocol designs (basket and umbrella designs). It is intended that this review will increase knowledge of these methods and promote their application in research.

***KEYWORDS:*** *Innovative approaches, Bayesian techniques, Adaptive designs, Clinical research*

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## INTRODUCTION

Clinical trials are research studies that put various human interventions—medical, surgical, or behavioral—to the test. Researchers mostly use these studies to ascertain whether novel forms of treatment or prevention, such as experimental medications, diets, or medical devices (such as pacemakers), are both safe and effective in humans. Clinical trials are used to find out whether an alternative treatment is more efficient or has fewer negative side effects than the standard of care.

The clinical trial design is an important aspect of interventional trials and is conducted with the best possible efficiency, ergonomics, and cost considerations.

The design of a clinical study is mostly concerned with strategy. The use of clinical trials as a method to answer scientific issues about breath research is crucial. Designing clinical studies strategically is the key to success. [1]

**The current state of clinical trial design and the need for novel approaches to improve efficiency and effectiveness:**

The highest degree of clinical evidence is provided by large randomized trials. Enrolling huge numbers of randomized patients across multiple trial sites, on the other hand, is costly and often takes years. There will never be enough traditional clinical studies to answer critical concerns. Efficient alternatives to traditional randomized trials that maintain bias and confounding precautions are thus of great interest. Novel trial designs are practical and can accommodate a large number of subjects at a low cost. [2]

## 1. ADAPTIVE DESIGNS

**Definition:** An adaptive design is defined as a design that allows modifications to the trial and/or statistical procedures after its initiation without undermining its validity and integrity. Clinical trials will be more flexible, efficient, and fast. Due to the level of flexibility involved, these trial designs are also termed as "flexible designs." [3]

**Overview of adaptive design:**

Pharma companies are gradually realizing that classically structured clinical trials are not flexible enough to use continuously emerging knowledge generated throughout a trial. Improved and innovative testing methods were developed to bridge the gap between basic scientific research and medical product development. It was done in order to ultimately

improve the discovery, development, and marketing of drugs.

Clinical trials using adaptive design methods are one of the innovations strongly recommended by the FDA. Additionally, the Bayesian approach could be used in clinical research and development.

Adaptation in clinical trials is intended to allow the investigator to determine the optimal health benefit of the treatment being tested. Neither validity nor integrity are compromised. Both regulatory agencies and industry have shown positive signals in adaptive design for clinical trials despite its infancy. [3]

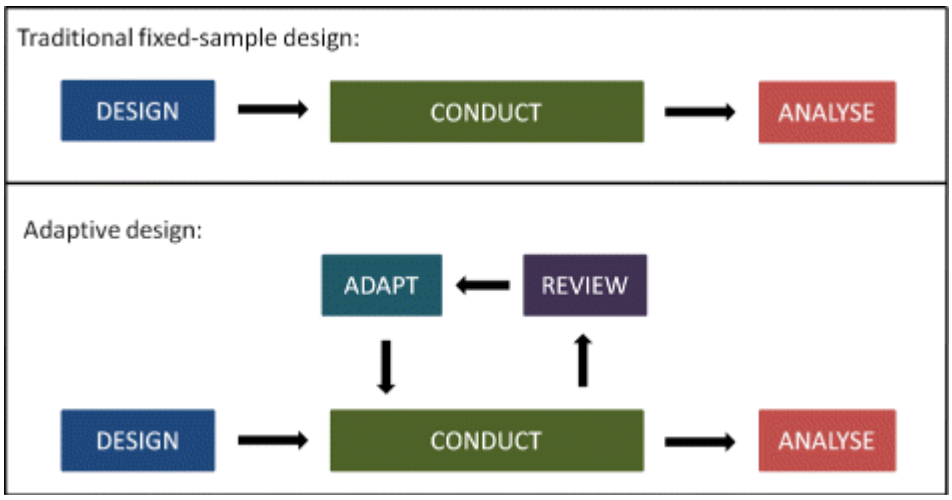


**Fig 1:Schematic of a traditional clinical trial design with fixed sample size, and an adaptive design with pre-specified review(s) and adaptation(s)**

**Types of adaptive designs:**

Based on adaptations employed, commonly considered adaptive design methods in clinical trials include

1. An adaptive randomization design,
2. A group sequential design,
3. A sample size re-estimation design,
4. A drop-the-loser design,
5. An adaptive dose-finding design,
6. A biomarker-adaptive design,
7. An adaptive treatment-switching design,
8. A hypothesis-adaptive design,
9. An adaptive seamless phase II/III trial design and
10. A multiple adaptive designs. [4]

**Advantages of adaptive design:**

- No protocol adjustments are required because any prospective modifications have already been accepted by ethics and regulatory committees.
- It is also possible to plan ahead for the logistics of changing therapies or doses.
- In addition, there is total flexibility for reacting to unanticipated situations, and alternatives exist to introduce any new doses or modify endpoints, among other things.
- Additionally, there is broad regulatory acceptance, particularly in the case of exploratory adaptive design clinical trials, and the results are kept credible by using blinded data or by using firewalls, where only a small number of individuals have access to the results.
- Despite the fact that many drug candidates eventually fail, these approaches enable earlier discovery and early termination of a clinical trial.
- Additionally, trial volunteers are used more effectively, and fewer individuals receive ineffective drugs, insufficient doses, or too high doses.
- Pharmaceutical companies can more swiftly redirect resources to other medications in their pipelines and waste less money on failing molecules.

**Disadvantages of adaptive designs:**

- Bayesian statistical methods are still considered nonstandard after adaptation, making them a compulsion rather than a choice when used for statistical analyses.
- In adaptive trials, it is sometimes difficult to control the type 1 error even after applying Bayesian statistical methods.

- Another risk is that ad hoc changes based on unblinded data may jeopardize the study's credibility.
- Even the EMEA's draft highlighted the possibility of damaging trial integrity due to frequent interim analyses.
- Also, there is a risk of attempting to adapt trials too early, jeopardizing the overall study results.
- Above all, blanket regulatory acceptance is still far away. [3]

## 2. BASKET AND UMBRELLA TRIALS:

A master protocol is a unifying study construct that includes multiple subgroups and sub studies, with patients having same or different diseases and that employ one or multiple drugs to treat it. Initially designed for oncology, master protocol trials are intended to simultaneously evaluate more than one investigational drug and/or more than one disease within the same overall trial structure. Master protocol design includes Basket and umbrella trials.

**Definition and differences between basket and umbrella trials** [5]

| Basket Trial | Umbrella Trial |
|---|---|
| ➢ A basket trial is a master protocol used to assess the efficacy of a single investigational medicine or therapeutic combination in various disease populations that are identified by the illness stage, histology, number of previous therapies, genetic or other biomarkers, or demographic features.<br>➢ Examples of basket trials<br>(1) A BRAF V600 study evaluating vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations (NCT01524978);<br>(2) KEYNOTE-158 evaluating pembrolizumab in patients with various types of advanced solid tumours who have progressed on standard of care of therapy (NCT02628067);<br>(3) NAVIGATE evaluating larotrectinib for the treatment of advanced solid tumours harbouring a fusion of neurotrophic tyrosine receptor kinase (NTRK) of types 1-3 (NCT02576431). | ➢ An umbrella trial is a general term for a master protocol created to assess many experimental medications provided as single medications or as medication combinations in a single disease group.<br>➢ Examples of umbrella studies<br>• For patients with NSCLC who have an EGFR mutation or an ALK gene, the National Cancer Institute is conducting a series of umbrella trials called ALCHEMIST (NCT04267848, etc.). |

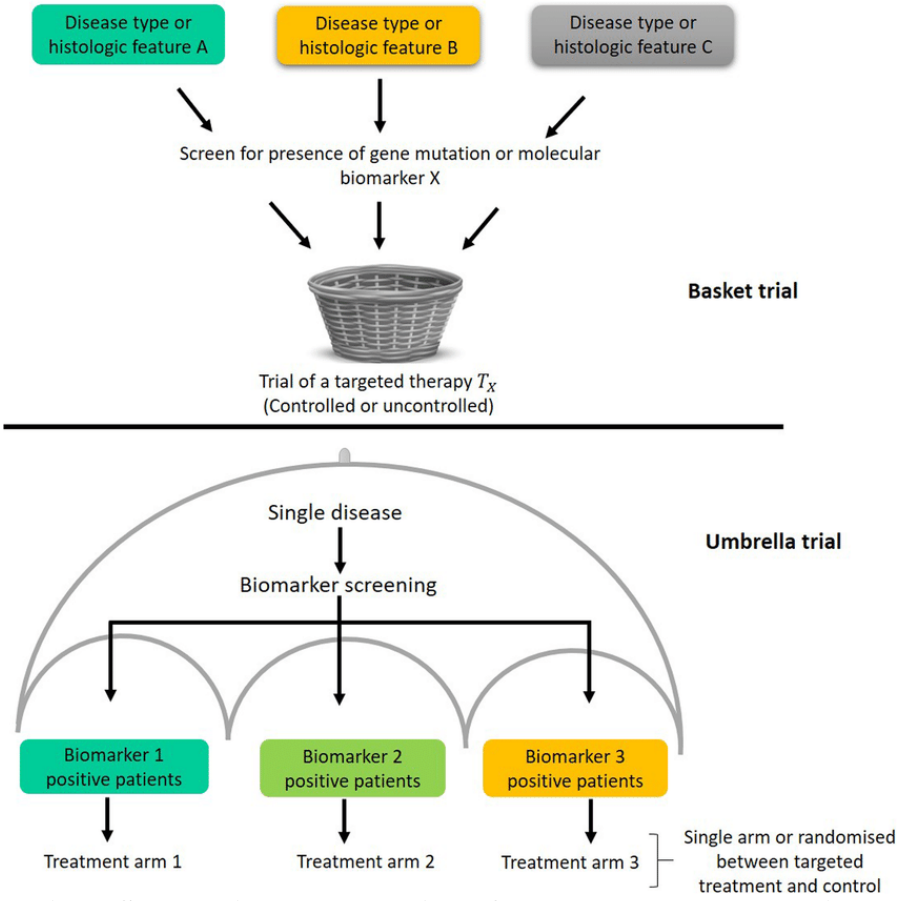


**Fig 2: Schematic representation of Basket and umbrella trials**

**Advantages and disadvantages of umbrella trials:**[5]

**Advantages:**

- Clustering different biomarkers under a single trial will help to reduce the screen failure rate, avoid multiple screening of patients, and increase the likelihood that a patient will be eligible to participate in a study.
- Enables a direct comparison of various treatment options for a disease.
- Because of their multifaceted approach, umbrella trials can speed up drug research, save expenses, and encourage quick clearance of novel medications (though regulatory acceptability varies by area).
- Increased operational effectiveness as a result of the separate arms' acquainted trial processes.

**Disadvantages:**

- Since treatment assignment/stratification is frequently based on molecular biomarkers, centralised screening tests are necessary for multiple biomarkers because locally performed genotyping can result in less reproducible results.
- Each new diagnostic biomarker needs to be validated.
- As new treatments become available, the standard of care for a disease may change over the course of extensive trials, possibly necessitating changes to the control arm's therapy, which could have an impact on statistical inferences.

**ADVANTAGES AND DISADVANTAGES OF BASKET TRIALS** [5]

**Advantages:**

- Quick identification of several possible therapeutic indications.
- Quick termination is possible for those arms where patients are showing low responses.
- Possible to investigate several rare diseases where patients' numbers are limited and collect more safety data than with individual trials.
- Exposure in multiple contexts can provide additional understanding of the mechanism of sensitivity and resistance of the target.
- Each trial requires the development/approval of only a single biomarker assay and this can often be tested locally at the sites.
- These trials can reach statistical power with fewer subjects in less time. If the treatment has already been approved for one disease, this design can rapidly verify if efficacy converts to other indications.
- Use of basket designs in areas where certain phenotypes are found across disease populations (e.g. patients with different types of pain) can increase the probability of technical success for a drug with a specific mechanism of action.
- Basket trials take less time than performing individual trials per indication, which can accelerate the speed of development, save costs and support rapid approval of new therapies.

**Disadvantages:**

- Various indications have different drug safety and drug doses.
- Potential issue of heterogeneity introduced by basket design.
- Challenges from a technical perspective in using the same trial endpoints across different diseases sharing the same biomarker.
- It requires multiple control arms to assess the benefit of therapy. This is because different types of standard of care and comparator treatments may be established for various diseases.
- It is difficult to evaluate some arms within a basket trial with small sample sizes. High treatment efficacy is a prerequisite to correctly determine whether the trial arms should be continued or discontinued and avoid selection bias based on chance findings in a few patients.
- Many patients must be tested to find the few who fit the disease profile targeted by the treatment. It is frustrating for patients who agree to be screened when they are told they are not eligible to be treated. This is because their disease profile does not match the drug target.
- The complexity of basket trials can present problems for ECs and investigators due to lengthy protocols (> 500 pages).
- Basket trials require several individual patient information leaflets and different informed consent forms for the various indications.
- Suitable principal investigators and facilities are required at each trial site to cover each indication in a basket trial, which is often difficult to realize.

## 3. OVERVIEW OF BAYESIAN METHODS

When using a Bayesian approach, the problem at hand must be formulated by defining the probability model and choosing the relevant parameter. Under the skeleton of Bayesian 1-2-3, applying the Bayesian approach is simple: defining the prior distribution of the parameter of interest; seeing the data; and updating the knowledge by calculating the posterior distribution. In order to design research questions and quantify the available data to provide answers to those questions, this offers a consistent and logical statistical framework. This method can be universally applied to simple and complex problems. [6]

**Advantages of Bayesian methods:**

- **Incorporation of prior information**

The Bayesian statistics contributes and improves the precision of the data from a current trial by including prior data, which is one benefit of using Bayesian approaches.

- **Adaptive trial design:**

In adaptive designs, accumulating data are used to adjust certain trial elements in accordance with a predetermined plan without compromising the trial's validity and integrity. Utilising Bayesian techniques makes it simpler to create adaptive trial designs.

- **Phase I dose-finding study**

The Continuous Reassessment Method (CRM) is a Bayesian methodology used to determine the maximum tolerated dose (MTD) of a drug molecule. A probability of toxicity is assigned to each dose, and a model is defined to represent the dose-response relationship. The CRM is flexible and allows different numbers of subjects to be treated per dose.

- **Phase II proof-of-concept studies**

The bayesian methodology can be used to improve decision-making in a proof-of-concept study, which is used to obtain early evidence of clinical efficacy using a small, targeted number of subjects.

- **Seamless phase II–III trials**

Phase II/III clinical trials can be integrated into a single confirmatory study, involving complex interim adaptations such as treatment selection, sample size reassessment, and stopping for futility. Bayesian predictive power can help make this decision-making process more efficient.

- **Decision can be taken in an efficient way**

Decisions can be taken in an efficient way by using bayasian methods

- **Postmarketing surveillance**

The Bayesian approach allows the use of premarketing data as a prior distribution for postmarketing surveillance.

- **Meta-analysis**

Bayesian statistics allows for meta-analysis of multiple data sets.[7]

**Disadvantages of Bayesian methods:**

- **Preplanning of design, conduct, and analysis of the trial**

Planning of design, conduct, and analysis is essential for a Bayesian trial to ensure scientific validity.

- **Mathematical modelling**

Extensive mathematical modeling of a clinical trial is involved in the Bayesian approach.

- **Computational issues**

Special computational algorithms are often used to analyze trial data, check model assumptions, assess prior probabilities at the design stage, perform simulations to assess the probabilities of various outcomes, and estimate sample size.

- **Ethical considerations:**

Implementation of Bayesian adaptive designs requires confidentiality of data to avoid operational biases, and Institutional Review Boards (IRBs) are needed to ensure the design is well planned and prespecified. [7]

## 4. PATIENT-CENTERED TRIALS:

Patient-centric trials are those that are planned and carried out with the patient in mind. This means conducting trials that are as convenient as possible for patients to participate in, such as using wearable or remote technology to cut down on clinic visits. Additionally, it entails integrating patients in the design of the research, for instance, to guarantee that the outcomes are pertinent and significant to the patients. Patient-centric trials aim to enhance the quality of research and its applicability to patients, hence enticing them to participate in trials.

**Principles of patient-centered trials:**

1. Respect for the patient's values, preferences, and expressed needs
2. Coordination and integration of care
3. Information and education
4. Physical comfort
5. Emotional support and alleviation of fear and anxiety
6. Involvement of family and friends
7. Continuity and transition
8. Access to care [8]

**Advantages of patient-centered trials:**

- **Patient-centric necessity eConsent:** eConsent reduces patient burden by allowing them to review consent documents at their own pace.
- **Direct-to-patient shipping** (DTP) is an advantage for patients who live far away or are too sick to travel, but it can be difficult to coordinate. Partners with experience and technical capabilities can help.
- **eCOA** is essential for patient-centric clinical trials, as it gives patients flexibility and enables study teams to collect data more frequently without overburdening them. It also reduces the risk of inconsistent or inaccurate data and lessens the workload for site monitors. [9]

**Disadvantages of patient-centric clinical trials:**

- Virtual trials are used in the majority of patient-centric trials.

- The biggest challenge is building trust.
- It requires a deep understanding of the digital ecosystem, which requires sponsors to invest in sophisticated technology.
- Some clinical research areas are not ready for remote monitoring.
- Diseases that require in-hospital monitoring are not appropriate for this approach.

## 5. BIG DATA & MACHINE LEARNING

### Overview of big data in clinical trials:

Any collection of data sets that is so huge and complicated that it becomes challenging to process using on-hand data management tools or conventional data processing programs is referred to as big data.

Big data has been incorporated into clinical practice for a while now, since before the information technology era began. Information technology makes it possible to store and extract medical records and follow-up data more effectively. A patient generates a lot of information right away after being admitted, including lab results, prescription information, fluid balance, progress notes, and imaging results.

Clinical researchers and doctors should make every effort to fully utilise the vast data that the EMR system and other healthcare databases are continuously producing. [10]

### Applications of big data in clinical trials:

- Big data are especially used in patient-centric clinical trials.

### Advantages of big data:

- Big data initiatives are essential for patient-centric care programs, providing insight into patients at greater risk for illness and encouraging them to take responsibility for their own wellness.
- Predictive analysis enables hospitals and other healthcare facilities to save money by accurately forecasting demand for medical supplies, which can be reinvested to yield higher profits.
- Big data can help reduce prescription error rates by analyzing patient records.
- Advancements in the healthcare sector are needed to enable rapid discovery of effective solutions and personalized solutions for health problems.
- Big data enables strategic planning by understanding people's motivations.
- Analytics helps prevent security threats by identifying changes in network traffic. [11]

### Overview of machine learning in clinical trials:

Artificial intelligence (AI) in the form of machine learning refers to algorithmic techniques that let computers solve issues without the need for specialized computer programming. In literature and popular media, the term "AI" is used very loosely to cover a wide range of promising applications, such as self-driving cars, digital personal assistants, and product personalization. [12]

### Applications of machine learning:

- Machine learning (ML) has a wide range of applications in clinical research, such as drug target identification, candidate molecule generation, and mechanism elucidation.
- ML can streamline the process and increase the success of drug target identification and candidate molecule generation through synthesis of existing research, elucidation of drug mechanisms, and predictive modeling of protein structures and future drug target interactions.
- Additionally, ML can synthesize and analyze enormous amounts of data to better elucidate the drug's mechanism.
- Furthermore, ML can optimize the choice of treatment regimens for testing.
- There are opportunities to use ML to improve the efficiency and yield of preclinical investigation and clinical trial planning. [13]

## 6. Overview of regulatory considerations for novel clinical trial designs

Recent meetings with Regulators and Ethics Committees have confirmed that they would like to be involved in the discussion of complex protocols with sponsors at an early time point. Currently some Health Authorities offer national scientific advice, but it would be desirable for a sponsor to have an EU-wide interaction with the Health Authorities in the countries foreseen for the conduct of a particular trial. Multi-national Pre-CTA consultations for complex/innovative trials is especially important to:

- Outline the protocol's endpoints and objectives in detail.
- Give participants the chance to ask questions, which aids in understanding the concerns of the national competent authority.
- Clearly state the ethical, scientific, and methodological basis for conducting the trial under a master protocol.
- Describe the selection of comparators/background therapy.
- Agree on the method for early termination of one arm.
- Describe the decision rules for stopping, expanding, or adding an arm.
- Discuss the role of DMCs (or other alternative bodies) with all the concerned member states.
- Be prepared for any big review obstacles. [5]

## CONCLUSION

Conventional clinical studies can never answer even a small portion of the most critical clinical issues. It is

becoming more common to adopt novel trial designs, some of which ignore or modify patient permission, to address research problems. There are also more and more modifications to traditional trial designs that add flexibility and efficiency. Many of the improvements we look at are appealing because they increase enrollment speed and decrease research costs. They also provide fresh difficulties in terms of preparation, behaviour, moral supervision, and statistical analysis.

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