PharmaSUG 2023 - Paper SA-228

Shifting the drug development paradigm with adaptive design and master protocol

Aman Bahl, Syneos Health®

ABSTRACT

Just as other industries have moved toward more flexible methodologies that foster continual improvement and operational efficiencies, the clinical development industry is slowly adopting innovative trial designs, after encouragement from regulatory agencies to speed progress, reduce inefficiencies, and improve success rates.

In recent years there has been a rise in more flexible trial designs compared to traditional adaptive and group sequential trials.

To get medicines to patients faster, clinical trials need to be more efficient, with fewer delays and lower costs. Adaptive trials, basket studies, platform trials, synthetic control arms and dose optimization studies are some of the options for achieving these goals.

Innovative clinical trial designs have the potential to shift the drug development paradigm towards more patient-centered, data-driven, and efficient approaches. These designs could improve patient outcomes, accelerate the availability of new treatments, and reduce the costs associated with drug development.

Risk-based approaches, which focus on quality-by-design and critical-to-quality factors, are now mandated by International Council for Harmonization (ICH) regulations, and clinical research 2.0, with its master protocols, adaptive designs, and synthetic arms, is changing the way trials are built, structured, and reported.

INTRODUCTION

Adaptive design and master protocols are two innovative approaches that are shifting the drug development paradigm by making clinical trials more efficient, flexible, and cost-effective.

Adaptive design allows for modifications to be made to an ongoing clinical trial based on data accumulated during the trial. This can involve changes to the sample size, dosing regimen, or even the inclusion criteria for the study. By using adaptive design, clinical trials can be more efficient, and the likelihood of success can increase.

Master protocols, on the other hand, involve the use of a single protocol that can be applied to multiple drugs or multiple indications. By using a master protocol, drug developers can streamline the clinical trial process, reducing the time and cost required to bring a new drug to market.

The combination of adaptive design and master protocols can have significant benefits for drug development. For example, the use of adaptive design can allow for faster decision-making, resulting in more efficient clinical trials. Additionally, the use of master protocols can allow for the simultaneous testing of multiple drugs or indications, which can lead to faster and more efficient drug development.

Overall, the use of adaptive design and master protocols represents a significant shift in the drug development paradigm, enabling a more efficient, flexible, and cost-effective approach to clinical trial design. This approach has the potential to accelerate the development of new drugs, benefiting patients and the healthcare industry.

ADAPTIVE DESIGN

Adaptive clinical trials are a type of clinical trial design that allows for modifications to be made to the trial protocol while the trial is ongoing. These modifications are based on accumulated data from the ongoing trial and are intended to improve the efficiency and precision of the trial.

Adaptive clinical trials differ from traditional clinical trials, which typically have a fixed study design that is determined before the trial begins and is not changed during the trial. In contrast, adaptive trials allow for changes to be made to the study design, such as the sample size, eligibility criteria, treatment regimen, or statistical analysis plan as shown in figure 1 below.

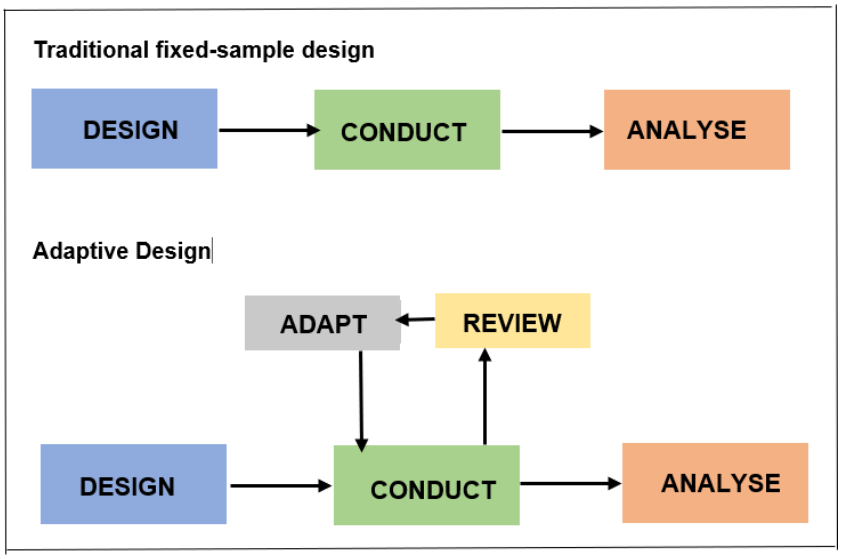

Figure 1: Traditional vs Adaptive design

CONVENTIONAL TRIAL VS ADAPTIVE DESIGN

Conventional clinical trials are typically designed with a fixed protocol that is defined at the start of the trial and remains unchanged throughout the trial. The protocol specifies the trial design, eligibility criteria, treatment regimen, endpoints, and statistical analysis plan. The trial is then conducted according to this fixed protocol, and any changes to the protocol require significant amendments and regulatory review.

On the other hand, adaptive clinical trials are designed to allow for modifications to the trial designs and protocols during the trials based on interim data analyses. Adaptive designs can incorporate pre-planned modifications, such as sample size re-estimation, dropping treatment arms that are not effective as well as unplanned modifications based on emerging data or safety concerns.

One of the main advantages of adaptive designs is that they can lead to more efficient and effective clinical trials. Adaptive designs can increase the likelihood of identifying a treatment effect and reduce the time and cost of conducting the trial. Adaptive designs can also help mitigate ethical concerns by reducing the number of patients who receive ineffective treatments.

The table 1 below shares the differences between conventional trials and those using adaptive designs.

Feature	**Conventional trial**	**Adaptive design**
Design	Rigid	Flexible
Treatment arms	Two or three at most	Multiple
Hypothesis	Test the hypothesis	Fit data into a hypothesis
Modifications	Protocol amendment required	Pre-specified changes allowed

Table 1: Conventional trial vs Adaptive design

ADAPTIVE CLINICAL TRIAL ADVANTAGE

Adaptive clinical trials have several advantages over traditional clinical trial designs. Here are some of the major advantages of adaptive clinical trials:

Increased efficiency: Adaptive clinical trials are designed to allow for ongoing modifications to the trial protocol based on interim data analyses, which can help optimize the trial design and increase efficiency by reducing the number of patients and resources required to achieve the trial objectives.

Faster results: The ability to modify the trial protocol in real-time based on interim data analyses can help speed up the clinical trial process and lead to faster results, which is particularly important for diseases with high morbidity and mortality rates.

Cost-effectiveness: Adaptive clinical trials can be more cost-effective than traditional clinical trial designs because they can be designed to reduce the duration of the trials, while still achieving the same or better trial objectives.

Increased likelihood of success: By allowing for ongoing modifications to the trial protocol, adaptive clinical trials can help improve the likelihood of trial success by optimizing the trial design and identifying the most effective interventions.

Overall, adaptive clinical trials have the potential to improve the efficiency and effectiveness of the clinical trial process, leading to faster results, improved patient outcomes, and cost savings for trial sponsors and healthcare systems.

TYPES OF ADAPTIVE DESIGN

There are several types of adaptive trial designs, including adaptive dose-finding, seamless phase I/II, adaptive randomization, and sample size re-estimation as shown in figure 2 below. Adaptive trials can also be designed to allow for futility or efficacy analyses at predetermined interim time points.

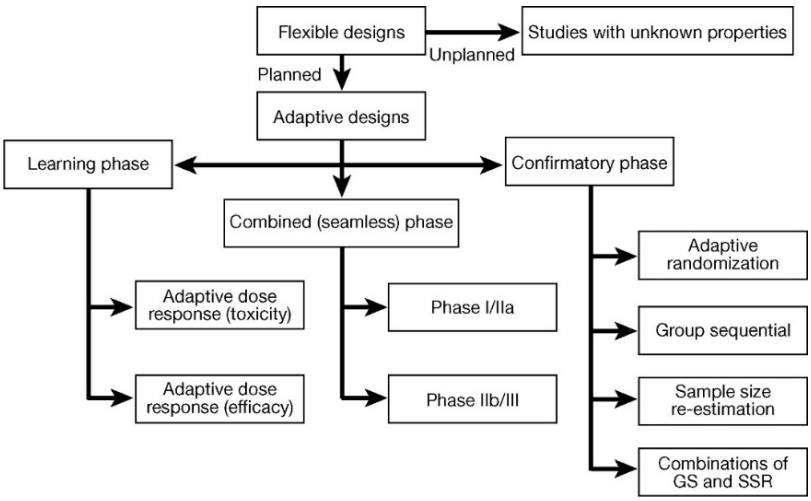

Figure 2: Types of Adaptive design [Ref:1]

Here are some of the most used adaptive design types:

Seamless phase II/III design: This design combines the phase II and III of a clinical trial into a single, continuous trial. This can save time and costs as well as help ensure that the best treatment regimen is identified as early as possible.

Adaptive dose-finding design: This design allows the dose of the experimental treatment to be modified during the trial based on the efficacy and safety data that accumulates as the trial progresses. This design is particularly useful when the optimal dose of the treatment is not known, or the dose-response

relationship is not clear.

Group sequential design: This design involves pre-planned interim analyses of the study data that are used to make decisions about stopping the trial early for futility or efficacy. This can help reduce the number of patients needed for the study and save time and costs. Group sequential trials are useful when there is a strong need for quick clinical decisions and policymaking and there are opportunities to do so (e.g., outcome data quickly observed for interim analyses). By stopping the trial early, the design can offer ethical, economic, and time-saving benefits.

Sample size re-estimation design: This design involves using the interim data from a trial to estimate the sample size needed to achieve the study's objectives. It is a type of adaptive trial where we can increase the sample size if required to ensure adequate power is maintained. In a sample size determination or initial sample size calculation, researchers are estimating what the initial sample size is. There are two primary types of sample size re-estimation (SSR). These are: unblinded sample size re-estimation and blinded sample size re-estimation. The difference between each type is in whether the data is blinded or not.

Adaptive randomization design: This design involves dynamically adjusting the allocation ratio of patients to the different treatment arms based on the accumulated data. This can help ensure that more patients are allocated to the better-performing treatment arm. There are two basic types of adaptive randomization design: covariate and response adaptive randomization.

A **biomarker-adaptive design** is a design that allows for adaptations using information obtained from biomarkers. A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic or pathogenic processes or pharmacologic response to a therapeutic intervention.

Other designs:

When trial designs do not contain a sufficient sample size and statistical power, alternative designs and analyses can allow research to proceed on the grounds that the research question has great clinical significance.

N-of-1 trials are multiple crossover trials done over time within a single person; they can also be done with a series of individuals. Their focus on the individual as the unit of analysis maintains statistical power while accommodating greater differences between patients than most standard clinical trials. This makes them particularly useful in rare diseases, while also being applicable across many health conditions and populations.

Adaptive trial designs are one such class of methods; they provide pre-planned opportunities to use accumulating trial participant outcome data to make changes to the course of the trial, whilst ensuring the statistical properties of the trial remain intact and results credible.

KEY DESIGN CONSIDERATIONS FOR ADAPTIVE CLINICAL TRIALS

Adaptive clinical trials require careful planning and execution to ensure that modifications made during the trial do not compromise the validity of the study results. Here are some key design considerations for adaptive clinical trials:

The choice of adaptive design: The type of adaptive design should be carefully considered based on the research question, the available data, and the objectives of the trial. The design should be chosen to optimize efficiency, precision, and safety monitoring.

The trial objectives: The trial objectives should be clearly defined and should be well-aligned with the adaptive design chosen. The objectives should be measurable, relevant, and achievable.

The study population: The study population should be carefully chosen to ensure that the trial results are generalizable to the population of interest. The inclusion and exclusion criteria should be carefully considered to ensure that the study population is representative of the intended patient population.

The study endpoints: The study endpoints should be clearly defined and should be chosen to reflect the research question and the treatment goals. The endpoints should be measurable and clinically relevant.

The sample size: The sample size should be carefully chosen to ensure that the trial has sufficient power to detect the treatment effect. The sample size should be based on statistical considerations, such as effect size, variability, and power.

The statistical methods: The statistical methods used in the trial should be carefully chosen to ensure that they are appropriate for the adaptive design chosen. The methods should be able to accommodate the modifications made during the trial without compromising the validity of the study results.

The interim analysis plan: The interim analysis plan should be carefully designed to ensure that the modifications made during the trial are based on sound statistical principles and do not compromise the validity of the study results.

The ethical considerations: The ethical considerations associated with the trial should be carefully considered and addressed. The trial should be conducted in a fair and equitable manner, and the participants should be fully informed of the trial objectives and any potential risks or benefits.

The regulatory considerations: The regulatory considerations associated with the trial should be carefully considered and addressed. The trial should comply with all relevant regulations and guidelines, and the regulatory authorities should be consulted early in the trial planning process.

Overall, adaptive clinical trials require careful consideration of a variety of design factors, including the choice of adaptive design, trial objectives, study population, endpoints, sample size, statistical methods, interim analysis plan, ethical considerations, and regulatory considerations. Careful planning and execution can help ensure that the trial is well-designed and that the modifications made during the trial do not compromise the validity of the study results.

USE CASES OF ADAPTIVE CLINICAL TRIALS

Adaptive clinical trials are a type of clinical trial design in which the trial is modified based on accumulating data during the trial. The goal of adaptive trials is to increase efficiency, reduce costs, and improve the chances of success while still maintaining scientific rigor.

Some of the use cases are as follows:

Precision Promise is PanCAN's groundbreaking service to accelerate new treatment options for pancreatic cancer patients. [Ref:2]

Advanced Biodesign starts first-in-human clinical trial targeting AML. [Ref:3]

The adaptive design proposed in ACTISAVE study optimizes the chances of proving glenzocimab efficacy for the benefit of patients who suffer from this dramatic condition. [Ref:4]

An 8-week regimen with bedaquiline and linezolid for rifampin-susceptible tuberculosis (TB) was found noninferior to the standard 6-months of treatment in an adaptive, open trial of several treatment strategies [Ref:5]

I-SPY 2 trial: This is a phase II clinical trial for breast cancer that uses an adaptive design to test multiple experimental drugs in combination with standard neoadjuvant therapy. The trial design allows for early identification of drugs that are most likely to be successful, which can then be advanced to larger phase III trials. [Ref:6]

REMAP-CAP trial: This is a phase II/III clinical trial for patients with severe community-acquired pneumonia (CAP) that uses an adaptive design to test multiple treatment options simultaneously. The trial design allows for the identification of the most effective treatment for each patient based on their individual characteristics. [Ref:7]

BATTLE trial: This is a phase II clinical trial for advanced stage lung cancer that uses an adaptive design to test multiple drugs and drug combinations. The trial design allows for the early identification of the most effective treatment options, which can then be advanced to larger phase III trials. [Ref:8]

Overall, these adaptive clinical trials demonstrate the potential benefits of using an adaptive design in clinical trials, including increased efficiency, improved chances of success, and more personalized treatment options for patients.

STATISTICAL ANALYSIS IN ADAPTIVE CLINICAL TRIALS

Statistical analyses play a crucial role in adaptive clinical trials. Adaptive clinical trials are designed to allow for changes to the trial design, such as sample size or treatment allocation, based on interim data analysis. Here are some common statistical analyses used in adaptive clinical trials:

Bayesian analysis: Bayesian analysis is a statistical technique used to update probabilities based on new data. Bayesian methods can be used in adaptive clinical trials to adjust the probability of success of a treatment, or the sample size based on interim data analysis.

Sequential analysis: Sequential analysis is a statistical technique used to analyze data as it is collected, rather than waiting until the end of the trial. Sequential analysis can be used in adaptive clinical trials to allow for interim analysis and modifications to the trial design.

Group sequential analysis: Group sequential analysis is a statistical technique used to allow for interim analysis and stopping rules in clinical trials. This technique involves dividing the trial into stages, with interim analyses conducted at predetermined points, allowing for early stopping of the trial if the treatment is shown to be effective.

Multiple testing procedures: Multiple testing procedures are statistical techniques used to adjust for the multiple comparisons that are made in clinical trials. In adaptive clinical trials, multiple testing procedures can be used to adjust for the multiple looks at the data that occur during the trial.

Simulation studies: Simulation studies are statistical techniques used to assess the power and sample size of a trial design. Simulation studies can be used in adaptive clinical trials to determine the optimal trial design and identify potential issues before the trial begins.

Overall, statistical analyses are crucial in adaptive clinical trials to ensure that the trial design is effective and that the results are reliable. The choice of statistical analysis will depend on the specific trial design and the data being collected.

ADAPTIVE CLINICAL TRIAL CHALLENGES

While adaptive clinical trials have several advantages over traditional clinical trial designs, they also present unique challenges. Here are some of the major challenges associated with adaptive clinical trials:

Complex trial design: Adaptive clinical trials require more complex trial design and statistical analysis, which can be challenging for researchers, regulatory agencies, and trial sponsors.

Increased regulatory oversight: Because adaptive clinical trials involve modifications to the trial protocol based on interim data analyses, they require increased regulatory oversight to ensure patient safety and trial integrity.

Operational challenges: Implementing adaptive clinical trials can be more operationally challenging than traditional clinical trials, as they require real-time monitoring of data and decision-making.

Resource-intensive: Adaptive clinical trials may require more resources, both in terms of funding and personnel, due to their more complex trial design and ongoing monitoring requirements.

Potential for bias: The adaptive nature of these trials may introduce potential for bias if the interim analyses are not conducted in a blinded or unbiased manner.

Communication challenges: Adaptive clinical trials may require more frequent communication between trial sponsors, regulatory agencies, and study sites to ensure that modifications to the trial protocol are properly implemented.

Overall, adaptive clinical trials have the potential to improve clinical trial efficiency and patient outcomes, but they require careful planning, monitoring, and oversight to ensure that they are conducted safely and effectively.

FDA AND ADAPTIVE DESIGNS

The FDA recognizes the potential benefits of adaptive designs and has issued guidance on the use of adaptive clinical trial designs in drug development. The FDA's guidance outlines the regulatory considerations and recommendations for the design, conduct, analysis, and reporting of adaptive clinical trials.

In 2018, the FDA released the guidance document "Adaptive Designs for Clinical Trials of Drugs and Biologics" which provides recommendations on the use of adaptive designs in drug development. [Ref:9] The guidance emphasizes the importance of early planning and communication with the FDA to ensure that the trial design is appropriate and meets regulatory standards. The guidance also highlights the need for appropriate statistical methods to minimize bias and maintain the integrity of the trial.

The FDA is also planning to further harmonise its guidance with regulators outside the US. The agency added a new item, “E20 Adaptive Clinical Trials,” which is currently being drafted by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) [Ref:10]

The FDA is supportive of the use of adaptive designs in clinical trials when they are properly designed, conducted, and monitored. The FDA recognizes the potential benefits of adaptive designs to speed up drug development and bring new treatments to patients in need more quickly, but it is important to ensure that these trials are conducted safely and effectively.

FUTURE OF ADAPTIVE DESIGN

The future of adaptive clinical trials is promising, as they offer several advantages over traditional clinical trials, including increased efficiency, reduced costs, and improved patient outcomes. Here are some potential future developments in adaptive clinical trials:

Increased use of Bayesian methods: Bayesian methods offer a flexible approach to designing and analyzing adaptive clinical trials. As computational power increases and software tools become more accessible, we can expect to see more widespread use of Bayesian methods in adaptive trials.

More complex designs: As researchers become more familiar with adaptive designs, we can expect to see more complex and innovative designs. For example, some researchers are exploring the use of adaptive trials in precision medicine, where the trial is designed to match patients with specific treatments based on their genetic or other biomarker profiles.

Use of real-world data: Adaptive trials can be designed to incorporate real-world data, such as electronic health records, to improve efficiency and reduce costs. As more healthcare data becomes available, we can expect to see more adaptive trials incorporating real-world data.

Greater regulatory acceptance: The FDA and other regulatory agencies have shown a willingness to accept adaptive trial designs, and we can expect to see more guidance and support for the use of adaptive trials in drug development.

Integration of digital technologies: Digital technologies, such as wearables and mobile health apps, can be integrated into adaptive trials to provide real-time monitoring of patient health and improve patient engagement. As these technologies become more widespread, we can expect to see more adaptive trials incorporating them.

Overall, the future of adaptive clinical trials is promising, and we can expect to see continued growth and innovation in this area.

One of the most promising ways to make drug development more efficient while enabling providers and patients to get better information about how a new medicine works is with more modern approaches to the design of clinical trials. One such approach is master protocol designs.

MASTER PROTOCOL

A master protocol is defined as a protocol designed with multiple sub-studies, which involve coordinated efforts to evaluate one or more investigational drugs, in one or more disease subtypes, with one or more objectives, all within the same overall trial structure.

Master protocols, being a collaborative approach to drug development, could help biopharma companies derisk research programs, improve the quality of evidence, and enhance R&D productivity by cutting down research costs and time.

MASTER PROTOCOL ADVANTAGE

Master protocols have several advantages over traditional clinical trial designs. Here are some of the major advantages of master protocols:

Increased efficiency: Master protocols allow for the simultaneous testing of multiple treatments or diseases within a single trial, which can increase trial efficiency by reducing the number of patients and resources required to achieve the trial objectives.

Faster results: By allowing for the simultaneous testing of multiple treatments or diseases, master protocols can lead to faster results and accelerate the development of new treatments.

Cost-effectiveness: Master protocols can be more cost-effective than traditional clinical trial designs because they can test multiple treatments or diseases within a single trial, while still achieving the same or better trial objectives.

Flexibility: Master protocols can be designed to allow for modifications to the trial protocol based on interim data analyses, similar to adaptive clinical trial designs, which can help optimize the trial design and increase efficiency.

Overall, master protocols have the potential to improve the efficiency and effectiveness of the clinical trial process, leading to faster results, improved patient outcomes, and cost savings for trial sponsors and healthcare systems.

FDA AND MASTER PROTOCOL

The FDA has also issued guidance on the use of master protocols in clinical trials. In 2018, the FDA released a draft guidance document titled "Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics" which provides recommendations on the use of master protocols in oncology clinical trials. [Ref:11]

The guidance outlines the regulatory considerations and recommendations for the design, conduct, analysis, and reporting of master protocol trials, including the need for clear study objectives, appropriate endpoints, and proper control groups. The guidance also highlights the importance of early communication with the FDA to ensure that the trial design is appropriate and meets regulatory standards.

The FDA encourages the use of master protocols in clinical trials when they are properly designed, conducted, and monitored. The FDA notes that master protocols can be particularly useful in the development of oncology drugs and biologics, where there is a need for more efficient and effective trial designs. However, it is important to ensure that these trials are conducted safely and effectively, with appropriate oversight and regulatory compliance.

KEY CHARACTERISTICS OF MASTER PROTOCOL RESEARCH PROGRAMS (MPRPS)

A master protocol is conducted with a collection of trials or sub studies that share key design components and operational aspects to achieve better coordination than can be achieved in single trials designed and conducted independently.

MPRPs have been used to investigate many interventions for a specific disease with an umbrella or platform design, as well as various interventions that target a specific genetic subtype of tumor independent of cancer type with a basket design. MPRPs can use bayesian or other adaptive techniques for assigning participants after screening to sub studies or for determining when a sub study should end. [Ref:12]

Master protocols that are well designed and executed can accelerate drug development by maximizing the amount of information obtained from the research effort. These trials can be updated to incorporate new scientific information, as medical science advances. Master protocols also reduce administrative costs and time associated with starting up new trial sites for each investigational drug. They can also increase data quality and efficiency through shared and reusable infrastructure. These advantages are of particular importance during a public health emergency such as the current SARS-CoV-2 pandemic, where there is a critical need for efficient drug development.

The FDA expects master protocols to continue to play an important role in addressing the public health needs created by the pandemic and in generating clinical evidence in general.

Following are the three types of Master protocols that we will be discussing in detail in the paper as shown in figure 3 below:

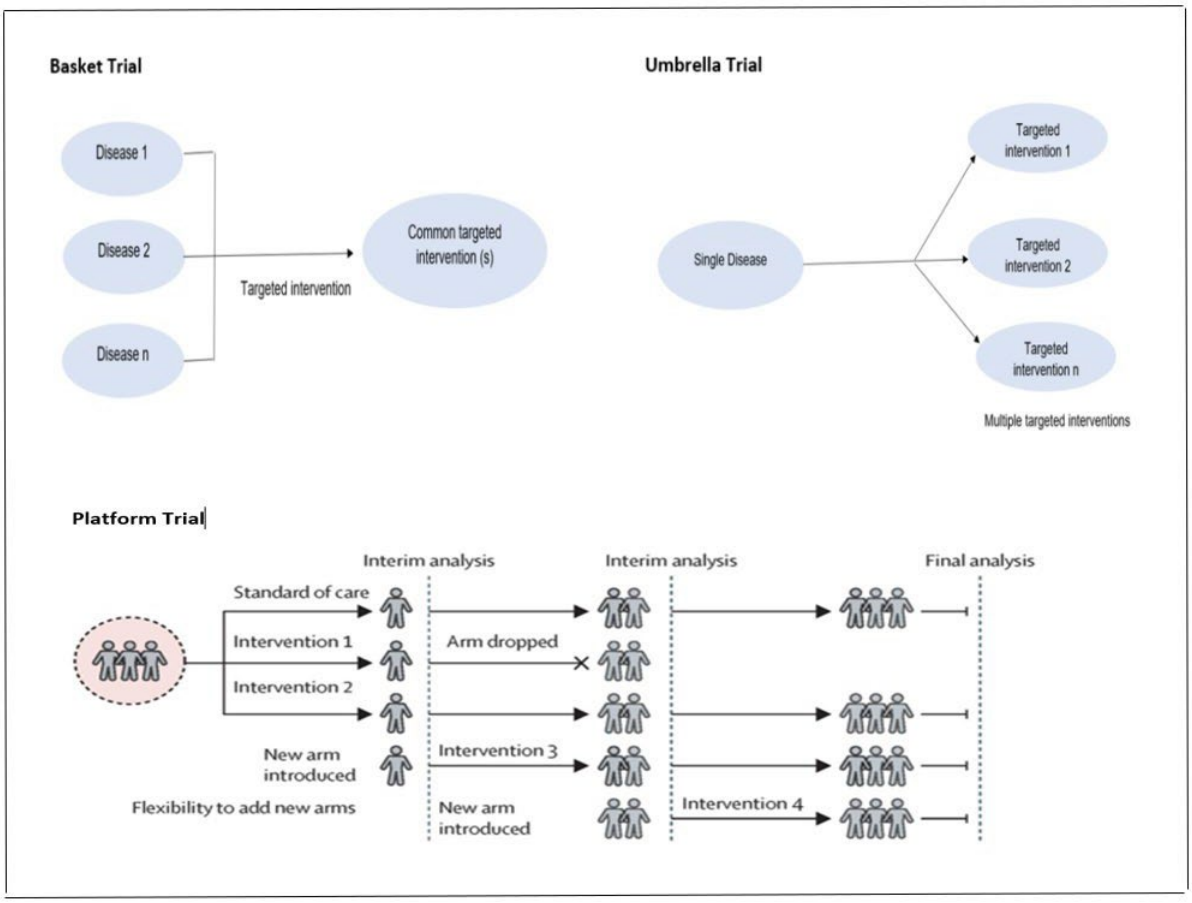

Figure 3: Types of Master Protocol

Basket designs are intended to study a single investigational regimen in several different diseases or disease subtypes.

Umbrella trial looks at multiple targeted therapies against the same disease as subgroups of one overall study population.

In **Platform trials**, studies are designed to assess multiple targeted therapies in the same study population, amending the protocol design when the ongoing data interpretation indicates that either an ineffective or efficacy threshold is reached.

Examples of MPRP study designs and substudies

- Umbrella design: Adjuvant Lung Cancer enricHmEnt Marker Identification and Sequencing Trials (ALCHEMIST) (eg, NCT02193282), erlotinib hydrochloride for early-stage non-small cell lung cancer) [Ref:13]
- Platform design: Randomised Evaluation of COVid-19 thErRapY (RECOVERY) (NCT04381936), which efficiently adds and removes specific interventions being studied for covid-19 based on decision algorithm [Ref:14]
- Basket design: US National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) (eg, NCT04439279), MATCH-Subprotocol R involving trametinib for cancers with BRAF mutations and fusions [Ref:15]

KEY CHARACTERISTICS OF MASTER PROTOCOL

Master protocols are clinical trial designs that allow for the evaluation of multiple interventions (such as drugs, drug combinations, or disease indications) in a single overarching protocol. Here are some key characteristics of master protocols:

Multiple sub-studies: Master protocols include multiple sub-studies, each evaluating a different intervention, within a single overarching protocol. This allows for the simultaneous evaluation of multiple interventions, which can reduce the time and cost of clinical trials.

Shared control group: Master protocols often use a shared control group for all the sub-studies, which can reduce the number of patients required for the trial and improve the efficiency of the trial design.

Adaptive design: Many master protocols use adaptive trial designs, which allow for modifications to be made to the trial design based on the accumulating data. This can improve the efficiency of the trial design by allowing for interventions to be added or removed based on their effectiveness.

Stratification: Master protocols often use stratification to ensure that patients are assigned to sub-studies based on their disease characteristics, such as molecular biomarkers or disease stage. This can increase the precision of the trial results by ensuring that patients are assigned to the most appropriate sub-study.

Data sharing: Master protocols often require data sharing among the sub-studies to ensure that the trial results are integrated and that the overall trial objectives are achieved. This can improve the efficiency and accuracy of the trial results by allowing for the pooling of data across sub-studies.

Overall, master protocols are designed to be flexible, efficient, and cost-effective, allowing for the simultaneous evaluation of multiple interventions within a single overarching protocol. By using a shared control group, adaptive trial design, stratification, and data sharing, master protocols can increase the precision and efficiency of clinical trials and accelerate the development of new treatments.

TYPES OF MASTER PROTOCOL

There are several types of master protocols used in clinical trials, including:

Platform trial: A platform trial is a type of master protocol that allows for the evaluation of multiple interventions in a single overarching protocol. Platform trials are designed to be flexible, allowing for the addition or removal of interventions based on the accumulating data. They are often used to evaluate interventions for multiple disease indications.

Basket trial: A basket trial is a type of master protocol that evaluates the effectiveness of a single intervention across multiple disease indications. Patients with different types of cancer, for example, may be enrolled in a single trial to evaluate the effectiveness of a single drug.

Umbrella trial: An umbrella trial is a type of master protocol that evaluates the effectiveness of multiple interventions for a single disease indication. Patients with a specific type of cancer, for example, may be enrolled in a single trial to evaluate the effectiveness of multiple drugs or drug combinations.

Adaptive platform trial: An adaptive platform trial is a type of master protocol that uses an adaptive trial design to allow for modifications to be made to the trial design based on the accumulating data. The trial may evaluate multiple interventions for a single disease indication or multiple disease indications.

Basket umbrella trial: A basket umbrella trial is a hybrid trial design that combines elements of both basket and umbrella trials. It allows for the evaluation of multiple interventions across multiple disease indications, providing greater flexibility and efficiency in the trial design.

Overall, the choice of master protocol depends on the research question and the specific interventions being evaluated. Each type of master protocol has its own advantages and disadvantages, and the choice of protocol will depend on the specific goals of the trial.

EXAMPLES OF BASKET TRIAL

Basket trials are a type of master protocol that evaluate the effectiveness of a single intervention across multiple disease indications. Here are some examples of basket trials:

NCI-MATCH trial: The trial is designed to evaluate the effectiveness of targeted therapies across multiple cancer types as discussed under MPRP section above [Ref:15]

MyPathway trial: The MyPathway trial is a basket trial that evaluates the effectiveness of a targeted therapy called pertuzumab in patients with advanced solid tumors. The trial is designed to evaluate the effectiveness of pertuzumab in patients with different types of tumors that have a specific genetic mutation. [Ref:16]

TAPUR trial: The Targeted Agent and Profiling Utilization Registry (TAPUR) trial is a basket trial that evaluates the effectiveness of targeted therapies in patients with advanced cancer. The trial is designed to evaluate the effectiveness of targeted therapies across multiple tumor types and genetic mutations. [Ref:17]

Overall, basket trials are a promising approach to evaluating the effectiveness of targeted therapies across multiple disease indications, allowing for a more efficient and cost-effective approach to clinical trial design.

EXAMPLES OF UMBRELLA TRIAL

Umbrella trials are a type of master protocol that evaluate the effectiveness of multiple interventions for a single disease indication. Here are some examples of umbrella trials:

Lung-MAP trial: The Lung-MAP trial is an umbrella trial that evaluates the effectiveness of targeted therapies in patients with advanced non-small cell lung cancer. The trial is designed to evaluate the effectiveness of multiple targeted therapies in patients with different genetic mutations. [Ref:18]

AML-MATCH trial: The AML-MATCH trial is an umbrella trial that evaluates the effectiveness of targeted therapies in patients with acute myeloid leukemia (AML). The trial is designed to evaluate the effectiveness of multiple targeted therapies in patients with different genetic mutations. [Ref:19]

MASTERPLAN trial: The MASTERPLAN trial is an umbrella trial that evaluates the effectiveness of multiple targeted therapies in patients with metastatic colorectal cancer. The trial is designed to evaluate the effectiveness of targeted therapies in patients with different genetic mutations. [Ref:20]

Overall, umbrella trials allow for the evaluation of multiple interventions for a single disease indication, providing a more efficient and cost-effective approach to clinical trial design. They also allow for the identification of subgroups of patients who may benefit from specific interventions, which can lead to more personalized treatment approaches.

EXAMPLES OF PLATFORM TRIALS

Examples of platform trials

Platform trials are a type of master protocol that allows for the evaluation of multiple interventions in a single overarching protocol. Here are some examples of platform trials:

Here are some use cases examples of platform trials:

COVID-19 treatments: The COVID-19 pandemic has accelerated the use of platform trials to test multiple treatments for the virus. The World Health Organization (WHO) launched the Solidarity trial [Ref:21], a platform trial that tested four potential treatments for COVID-19, including remdesivir, hydroxychloroquine, lopinavir/ritonavir, and interferon-beta.

Cancer treatments: Platform trials have been used in oncology to test multiple drugs or drug combinations for different types of cancer. For example, the Lung-MAP trial [Ref:18] is a platform trial that tests multiple treatments for lung cancer, while the I-SPY 2 trial [Ref:6] is testing different treatments for breast cancer.

Rare diseases: Platform trials can also be useful in testing treatments for rare diseases. The platform trial, called Beat SCAD, is a global study aimed at finding an effective treatment for spontaneous coronary artery dissection (SCAD), a rare and poorly understood condition that can cause heart attacks. [Ref:22]

Alzheimer's disease: Platform trials are also being used to test treatments for Alzheimer's disease, a condition that has proven difficult to treat. The Alzheimer's Disease Cooperative Study (ADCS) platform trial is a clinical trial that aims to test multiple treatments for mild-to-moderate Alzheimer's disease. The trial, also known as the Alzheimer's Clinical Trial Consortium (ACTC) trial, is designed to test multiple treatments simultaneously using a shared infrastructure, allowing for more efficient and cost-effective drug development. [Ref:23]

Infectious diseases: Platform trials are also being used to test treatments for infectious diseases such as HIV, tuberculosis, and hepatitis C. The AIDS Clinical Trials Group (ACTG) is conducting a platform trial to test multiple treatments for HIV, while the PanACEA trial is testing different treatments for tuberculosis. [Ref:24]

Platform trials are a promising approach to evaluating the effectiveness of multiple interventions in a single protocol, providing a more efficient and cost-effective approach to clinical trial design. They also allow for the identification of subgroups of patients who may benefit from specific interventions, which can lead to more personalized treatment approaches.

AREAS OF USE FOR PLATFORM TRIALS

BASKET TRIALS

Here are some of the areas of use for basket trials:

Precision medicine: Basket trials allow for a more personalized approach to cancer treatment by targeting patients who share a specific genetic mutation or biomarker, rather than just their cancer type. This precision medicine approach may lead to more effective treatments and better outcomes for patients.

Drug development: Basket trials can help pharmaceutical companies identify new uses for existing drugs or new drugs that target specific genetic mutations or biomarkers. This can accelerate drug development and lead to faster approvals for new treatments.

Clinical trial efficiency: Basket trials can be more efficient than traditional clinical trials because they allow for the evaluation of multiple cancer types in a single trial. This can reduce the time and cost of conducting multiple trials for different cancer types.

Rare cancers: Basket trials can be particularly useful for rare cancers, which often have limited treatment options and a small patient population. By including multiple cancer types in a single trial, basket trials can increase the number of patients eligible for the trial and improve the chances of identifying effective treatments.

Overall, basket trials have the potential to revolutionize cancer treatment by targeting specific genetic mutations or biomarkers and allowing for a more personalized approach to treatment. As more pharmaceutical companies and researchers explore the use of basket trials, we may see more areas of use and potential benefits emerge.

UMBRELLA CLINICAL TRIALS

Here are some of the areas of use of umbrella clinical trials:

Precision medicine: Like basket trials, umbrella trials allow for a more personalized approach to disease treatment by targeting patients who share a specific genetic mutation or disease subtype, rather than just their disease type. This precision medicine approach may lead to more effective treatments and better outcomes for patients.

Drug development: Umbrella trials can help pharmaceutical companies identify new uses for existing drugs or new drugs that target specific disease subtypes or genetic mutations. This can accelerate drug development and lead to faster approvals for new treatments.

Clinical trial efficiency: Umbrella trials can be more efficient than traditional clinical trials because they allow for the evaluation of multiple disease subtypes or genetic mutations in a single trial. This can reduce the time and cost of conducting multiple trials for different disease subtypes.

Rare diseases: Umbrella trials can be particularly useful for rare diseases, which often have limited treatment options and a small patient population. By including multiple disease subtypes in a single trial, umbrella trials can increase the number of patients eligible for the trial and improve the chances of identifying effective treatments.

Regulatory approval: Umbrella trials can help streamline the regulatory approval process by providing a more comprehensive evaluation of a drug's effectiveness across multiple disease subtypes or genetic mutations. This can help pharmaceutical companies obtain faster regulatory approval for new treatments.

PLATFORM TRIALS

Here are some of the areas of use of platform clinical trials:

Rapid evaluation of interventions: Platform trials allow for the evaluation of multiple interventions or treatments for a specific disease or condition in a single trial. This can accelerate the pace of research and drug development by allowing researchers to quickly evaluate the effectiveness of multiple treatments.

Adaptive trial design: Platform trials often use an adaptive trial design, which allows researchers to modify the trial design as new information becomes available. This can help ensure that the trial remains relevant and effective over time.

Patient-centered approach: Platform trials typically use a patient-centered approach to trial design, which can improve patient recruitment and retention. By involving patients and patient advocacy groups in trial design and decision-making, researchers can ensure that the trial is designed with the patient's needs in mind.

More efficient use of resources: Platform trials can be more efficient than traditional clinical trials because they allow for the evaluation of multiple interventions or treatments in a single trial. This can reduce the time and cost of conducting multiple trials for different interventions.

Rapid response to new information: Platform trials can be designed to respond quickly to new information, such as the emergence of new treatments or changes in disease prevalence. This can help ensure that the trial remains relevant and effective over time.

MASTER PROTOCL CHALLENGES

Master protocols also present unique challenges compared to traditional clinical trial designs. Here are some of the major challenges associated with master protocols:

Complex trial design: Master protocols require more complex trial design and statistical analysis, which can be challenging for researchers, regulatory agencies, and trial sponsors.

Increased regulatory oversight: Because master protocols involve testing multiple treatments or diseases within a single trial, they require increased regulatory oversight to ensure patient safety and trial integrity.

Operational challenges: Implementing master protocols can be more operationally challenging than traditional clinical trials, as they require coordination among multiple stakeholders, including trial sponsors, investigators, regulatory agencies, and study sites.

Resource-intensive: Master protocols may require more resources, both in terms of funding and personnel, due to their more complex trial design and ongoing coordination requirements.

Potential for bias: The master protocol design may introduce potential for bias if the study design is not properly controlled, randomized, or blinded.

Communication challenges: Master protocols may require more frequent communication among trial sponsors, regulatory agencies, and study sites to ensure that modifications to the trial protocol are properly implemented.

Overall, master protocols have the potential to improve clinical trial efficiency and patient outcomes, but they require careful planning, monitoring, and oversight to ensure that they are conducted safely and effectively. Properly designed master protocols can offer tremendous opportunities for efficient clinical research, but they need to be implemented with care to avoid unintended consequences such as an increase in costs, delays in study completion or risk to patient safety.

FUTURE OF MASTER PROTOCOL

The use of master protocols in clinical trials is expected to grow in the future as it offers several benefits over traditional trial designs. Some of the potential future developments in the use of master protocols are:

Expansion into new therapeutic areas: Master protocols have primarily been used in oncology clinical trials. However, there is growing interest in applying this approach to other therapeutic areas, such as neurology, infectious diseases, and rare diseases.

Use of adaptive trial designs: Master protocols can incorporate adaptive designs, which allow for modifications to the trial based on accumulating data. This approach can improve trial efficiency and reduce the overall time and cost required for drug development.

Integration with real-world data: The integration of real-world data into master protocols can provide additional information on patient outcomes, treatment patterns, and adverse events. This approach can enhance the overall understanding of the efficacy and safety of the intervention being tested.

Collaboration between stakeholders: The use of master protocols encourages collaboration between stakeholders, including pharmaceutical companies, regulatory agencies, academic institutions, and patient advocacy groups. This collaboration can enhance the design and conduct of clinical trials and improve the likelihood of success.

Overall, the future of master protocols is promising as it offers a more efficient and cost-effective approach to drug development while maintaining high levels of scientific rigor. The continued adoption and refinement of master protocols will likely lead to more successful clinical trials and improved patient outcomes.

CONCLUSION

Innovative clinical trial designs have the potential to shift the drug development paradigm in several ways, by improving the efficiency, speed, and accuracy of drug development. Some of the ways in which innovative clinical trial designs could shift the drug development paradigm include:

Reducing costs and time: Innovative clinical trial designs such as adaptive trials, platform trials, and master protocols have the potential to reduce the costs and time required for drug development. By allowing for more efficient testing of multiple treatments in a single trial or adapting the trial design based on emerging data, these designs could accelerate the identification of effective treatments and reduce the costs associated with unsuccessful trials.

Identifying patient subgroups: Innovative clinical trial designs such as umbrella trials and basket trials could improve the identification of patient subgroups that are most likely to benefit from a given therapy. By testing multiple treatments in a single trial or evaluating the effectiveness of a single drug across multiple cancer types, these designs could enable more personalized medicine approaches that better match treatments to individual patients.

Increasing patient engagement: Innovative clinical trial designs such as decentralized trials and N-of-1 trials could increase patient engagement and participation in drug development. By allowing for remote data collection and patient monitoring or personalized medicine approaches that involve individual patients serving as their own control group, these designs could improve patient experiences and reduce the burden associated with traditional clinical trials.

Enhancing data collection and analysis: Innovative clinical trial designs such as platform trials and adaptive trials could improve data collection and analysis, by incorporating digital technologies such as artificial intelligence and machine learning. By automating data collection and analysis, these designs could accelerate the identification of effective treatments and reduce errors associated with manual data entry and analysis.

Overall, innovative clinical trial designs have the potential to shift the drug development paradigm towards more patient-centered, data-driven, and efficient approaches. These designs could improve patient outcomes, accelerate the availability of new treatments, and reduce the costs associated with drug development. However, it is important to note that the development and implementation of new trial designs will require collaboration between researchers, regulators, and industry stakeholders to ensure that they are safe, ethical, and scientifically rigorous.

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ACKNOWLEDGMENTS

Sincere thanks to my Syneos Health senior management team including **Sandra Vermeulen**, VP, Global FSP 360, **X.Q Xue**, Vice President, Biostatistics, **Dan Strieter**, Senior Director, Biostatistics and **Andrew Cross**, Director, Biostatistics for their vision, great leadership, persistent support, and encouragement to make this paper possible.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Aman Bahl
Associate Director, Statistical Programming, Clinical Division, Syneos Health
Phone: +1-905-399-6715
E-mail: Aman.Bahl@syneoshealth.com
Web: http://www.syneoshealth.com