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Review

Evolution and Best Practices in Clinical Trials Design: A Review

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ABSTRACT:

A Clinical trial is a research study in human volunteers to answer specific health questions carefully conducted clinical trials are fastest and safest way to find treatment that work in people and way to improve health. Clinical research is an alternative terminology used to describe medical research clinical research `involves people and it is generally carried out to evaluate the efficacy of therapeutic drug a medical surgical, or a device as a part of treatment and patient management. Clinical trials are the gold standard for evaluating the efficacy and safety of new treatments. Well-designed trials ensure reliable results, while poorly designed trials can lead to biased or inconclusive outcomes. This review article discusses the fundamentals principles, recent advancements, and best practices in clinical trial design.

KEYWORDS: Clinical trial design and best practices of clinical trial design.

INTRODUCTION:

1. DEFINTION:

Clinical trial is defined as "a systematic study of new drug(s) in human subject(s) to generate data for discovering and/or verifying the clinical, pharmacological (including pharmacodynamic and pharmacokinetic) and/or adverse effects with the objective of determining safety and/or efficacy of the new drug". [1]

Clinical trials help in determining if a new intervention works ,its safety & efficacy and is it better than already available treatments. According to WHO define clinical trial as : "Any research study that prospectively assign human participants or group of humans to one or more health related interventions to evaluate the effects on health outcomes".[2]

Clinical trials are a fundamental component of medical research. Before any treatment is approved and offered to patients in the general population, rigorous evidence of its safety and efficacy must be reported. Clinical trials are the main route to obtain this required evidence. In this article, we present some general principles of good clinical trial design, which are often used as the basis to evaluate the quality of the evidence presented in manuscripts reporting trial results.[3]

2 .CLNICAL TRIAL DESIGN:

Clinical research, our aim is to a study, which would be able to derive a valid and meaningful scientific conclusion using appropriate statistical methods that can be translated to the "real world" setting. Before choosing a study design, one must establish aims and objectives of the study, and choose an appropriate target population that is most representative of the population being studied. The conclusions derived from a research study can either improve health care or result in inadvertent harm to patients. Hence, this requires a well-designed clinical research study that rests on a strong foundation of a detailed methodology and is governed by ethical principles.

"From an epidemiological standpoint, there are two major types of clinical study designs, observational and experimental. Observational studies are hypothesis-generating studies, and they can be further divided into descriptive and analytic. Descriptive observational studies provide a description of the exposure and/or the outcome, and analytic observational studies provide a measurement of the association between the exposure and the outcome. Experimental studies, on the other hand, are hypothesis testing studies. It involves an intervention that tests the association between the exposure and outcome. Each study design is different, and so it would be important to choose a design that would most appropriately answer the question in mind and provide the most valuable information.[4]

3. CLINICAL TRIAL PHASES :

A clinical trial is a systematic process that is intended to find out the safety and efficacy of a drug/device in treating/preventing/diagnosing a disease or a medical condition. Clinical trial includes various phases that include phase 0(micro-dosing studies), phase 1, phase 2, phase 3, and phase 4. Phase 0 and phase 2 are called exploratory trial phases, phase 1 is termed the non- therapeutic phase ,phase 3 is known as the therapeutic confirmatory phase , phase 4 is called the post -approval or the post marketing surveillance phase. [5]The implementation of clinical trials involves a rigorous approach founded on scientific, statistical, ethical, and legal considerations. Thus, it is crucial for health care providers to understand the precepts on which well-performed clinical trials rest in order to maintain a partnership with patients and industry in pursuit of the safest, and most effective and efficient therapies.[6]

4 . IMPORTANCE OF CLINICAL TRIALS :

1. Guiding Healthcare Decision-Making: Clinical trials provide high-quality evidence, informing Healthcare decisions, shaping medical guidelines, and optimizing resource allocation.[7]

2. Ensuring Safety and Efficacy: Clinical trials rigorously evaluate the safety and efficacy of new treatments, protecting patients from harm and ensuring that only effective treatments are adopted.[8]

3. Promoting Transparency and Accountability: Clinical trials foster transparency and accountability, enabling researchers, clinicians, and patients to make informed decisions.[9]

FUNDAMENTALS OF CLINICAL TRIALS DESIGN :

TYPES OF CLINICAL TRIALS :

Research study designs are classified into two types as follows:

1. Observational Study Designs In observational study the subjects or recruited population are just observed, as name indicates no interventions are taken place. Based on the time, observational study designs are further categorized into analytical study and descriptive study . And main goal of the various study designs include Descriptive study is to generate hypothesis, Analytical study is to test hypothesis and Experimental study is to prove hypothesis.

2. Experimental Study (Interventional Study) Experimental studies are not as the observational studies there is an intervention taken place. Thus, it is also named as Interventional study. The national institute of health (NIH) defined an interventional study as individual in which "participants receive specific interventions according to the research plan created by the investigators. These interventions may be medical products, such as drugs or devices; procedures; or changes to participants behaviour". Experimental study designs further classified into randomized controlled trials and non-randomized controlled trials.[10]

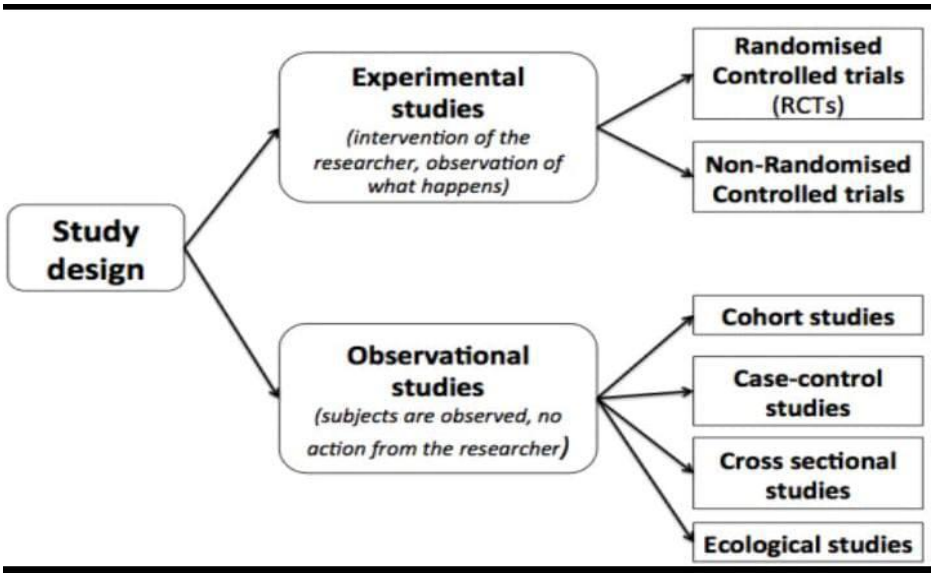

FIGURE :1 TYPES OF CLINICAL TRIALS DESIGN[10]

OBSERVATIONAL STUDY DESIGNS

Observational studies are those in which groups of individuals are monitored or outcomes are measured without manipulation or intervention to affect the result. Observational studies include case-control, cohort, and cross-sectional studies.

1. CASE - CONTROL STUDIES :

Individual observational studies that involve grouping of subjects based on selected outcomes are termed case-control studies. In these studies, the exposure experience of the case group (subjects with the outcome of interest) is compared

with that of the control group (subjects without the outcome), for instance occurrence or non-occurrence of renal failure in diabetic patients or heart attacks in hypertensive patients. The design of such studies is retrospective and evaluates possible associations between exposures and outcome. They are quick and inexpensive to perform, and the results are expressed as odds ratios (OR) and risk ratio/relative risk. Case control studies enable multiple exposure variables to be examined for a given outcome, but they do not allow correlation of sequential causes and effects with the outcome .

2. COHORT STUDIES :

This type of study subjects is grouped based on exposure. Cohort studies enable multiple outcomes to be studied for a given exposure. The exposure is well-defined, but the outcome may vary, thus providing an opportunity to monitor many outcomes of a single exposure . Cohort studies can be retrospective, where the cohorts are defined on the basis of a past exposure, or prospective, where the cohorts re defined by a current exposure.

A. Retrospective cohort studies:

In retrospective cohort observational studies, the researchers look back in time at archived or self-reported data in order to compare outcomes in exposed and non-exposed patients. The two groups are identified retrospectively and studied prospectively. This type of study is quick and inexpensive , but is prone to recall-bias.

B.Prospective cohort studies:

A prospective cohort study is a longitudinal cohort study in which cohorts differing in exposure to the factors being studied are followed up at predetermined time intervals to determine the effect on outcomes. This type of study helps to determine associations between a particular exposure and outcomes.

3.CROSS - SECTIONAL STUDIES :

Cross-sectional studies have transverse study design and involve concurrent assessment of exposures and outcomes without any follow-up. These studies are essentially based on surveys, and are therefore appropriate for determining prevalence but cannot shed light on causation .[11]

TABLE -1 Advantages and disadvantages of a case-control study, cohort study, case-control study within a defined cohort, and cross-sectional study [11]

Study type	Advantage	Disadvantage
Case-control study	Less expensive, less time-consuming	Vulnerable to bias (recall bias, selection bias, confounding bias)
	Good for the study of rare disease	
	Can assess multiple risk factors at once	
Cohort study	Effective to establish cause and effect	Possibility of selection bias, information bias
	Useful to identify the timeline over which certain exposures can contribution to outcome	More expensive, more time-consuming (prospective cohort study)
	Can collect a wide variety of data	Risk bias in sampling the cohort (retrospective cohort study)
Case-cohort study	The ability to study several diseases using the same sub-cohort	Require a more complicated statistical analysis
Cross-sectional study	Useful to assess the prevalence of disease	Cannot infer causality
	Can suggest a natural progression with less cost	Cannot estimate incidence rate
		Not good for studying rare disease
		Susceptible to non response bias and recall bias

2.Experimental Study (Interventional Study)

Experimental studies are not as the observational studies there is an intervention taken place. Thus, it is also named as interventional study. The national institute of health (NIH) defined an interventional study as individual in which "participants receive specific interventions according to the research plan created by the investigators. These interventions may be medical products, such as drugs or devices; procedures; or changes to participants behavior". Experimental study designs further classified as follows based on the randomization.[12]

A . RANDOMISED CONTROLLED TRIALS :

Randomized controlled trials (RCTs) are trials in which the subjects are randomly assigned to experimental and control groups. The experimental group is given the treatment that is being tested and the control group is given an alternative treatment or a placebo or no treatment at all. Most experimental clinical studies are RCTs, and the subjects are either

healthy volunteers or patients. After a new drug passes a pre-clinical trial, it is tested via RCTS. Various aspects of the RCT require careful consideration before the trial begins, for example study design, patient population, control group selection, randomization, sampling, blinding or open labelling of treatments and outcomes .[13]

B.NON-RANDOMISED CONTROLLED TRIALS :

Non-randomised studies that compared two or more strategies aimed at increasing participant retention in randomized trials. The retention trials had to be nested in real (i.e. not hypothetical) randomized 'host' trials, including feasibility studies. The most robust test of the effectiveness of a retention strategy is a trial comparing one retention method with an alternative, 'nested' within an ongoing host clinical trial. By 'nesting', we refer to patients being allocated to two or more alternative methods of retention by random or non-random methods. Such studies provide a context that is the same as the one we are interested in clinical trials. This makes judgements about the applicability of the evidence coming from these evaluations more straightforward than for evaluations done outside trials and/or outside health-care .[14]

PHASES OF CLINICAL TRIALS :

These phases are as following:

1) Phase I : Human/Clinical Pharmacology trial
2) Phase II : Exploratory trial
3) Phase III : Confirmatory trial
4) Phase IV : Post-Marketing Surveillance

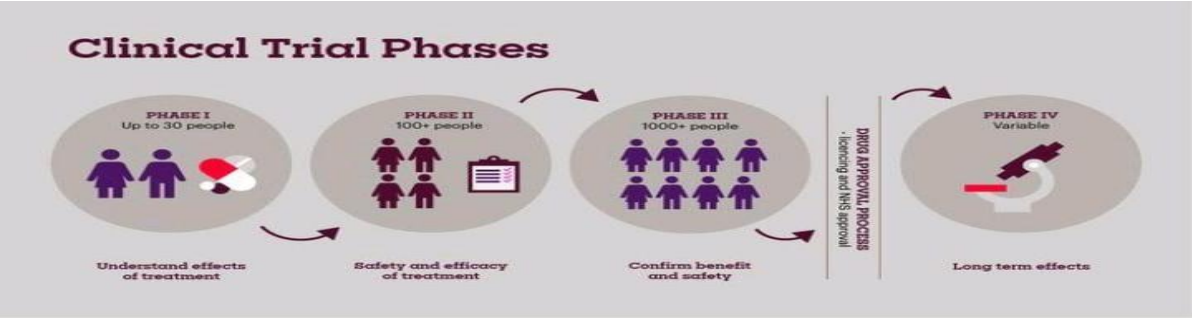

FIG 2: PHASES OF CLINICALTRIALS [15]

PHASE 0 :

Phase 0 is a recent designation for exploratory, first-in- human trials conducted in accordance with the U.S. Food and Drug Administration's (FDA) 2006 Guidance on Exploratory Investigational New Drug (IND) Studies Phase 0 trials are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in human subjects as was anticipated from preclinical studies. Distinctive features of Phase 0 trials include the administration of single sub therapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics (how the body processes the drug) and pharmacodynamics (how the drug works in the body).[16]

PHASE I :

Phase I trials are the first stage of testing in human subjects. Normally, a small (20-80) group of healthy volunteers will be selected. This phase includes trials designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics and pharmacodynamics of a drug. This phase also investigates the dose related side effects . about 70% of experimental drug pass this phase of testing . ref clinical trial general review .[17]

There are different kinds of Phase I trials

1. SAD [Single Ascending Dose]:

Single Ascending Dose studies are those in which small groups of subjects are given a single dose of the drug while they are observed and tested for a period of time. If they do not exhibit any adverse side effects, and the pharmacokinetic data is roughly in line with predicted safe values, the dose is escalated, and a new group of subjects is then given a higher dose. This is continued until pre-calculated pharmacokinetic safety levels are reached, or intolerable side effects start showing up at which point the drug is said to have reached the mad.

2.MAD (Maximum tolerated dose):

Multiple Ascending Dose studies are conducted to better understand the pharmacokinetics & pharmacodynamics of multiple doses of the drug.

PHASE II :

Phase II trials are performed on larger groups (20-300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments in a larger group of volunteers and patients. When the development process for a new

drug fails, this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects.

phase II trials are also important to collect additional safety data, determining drug dosing ranges, routes and timing for phase III trials, as well as common short-term adverse events. There are numerous phase II trials evaluating the efficacy of pharmacological agents .[18]

PHASE III :

Based on prior studies demonstrating drug safety and potential efficacy , a phase III (also referred to as a "therapeutic confirmatory," "comparative efficacy," or "pivotal trial") may be pursued. This stage of drug assessment is conducted in a larger and often more diverse target population in order to demonstrate an confirm efficacy and to identify and estimate the incidence of common adverse reactions. [19]

Based on prior studies demonstrating drug safety and potential efficacy , a phase III (also referred to as a "therapeutic confirmatory," "comparative efficacy," or "pivotal trial") may be pursued. This stage of drug assessment is conducted in a larger and often more diverse target population in order to demonstrate an confirm efficacy and to identify and estimate the incidence of common adverse reactions.

Most drugs undergoing Phase III clinical trials can be marketed under FDA norms with proper recommendations and guidelines, but in case of any adverse effects being reported anywhere, the drugs need to be recalled immediately from the market. While most pharmaceutical companies refrain from this practice, it is not abnormal to see many drugs undergoing Phase III clinical trials in the market.

PHASE IV :

A Phase IV trial, also referred to as a Post-Marketing Surveillance Trial, encompasses safety surveillance (pharmacovigilance) and continuous technical support for a drug once it has been authorized for sale. Although approved interventions typically bypass Phase IV trials, these studies can significantly enhance our understanding of the optimal usage patterns of a therapy, its varied adverse event profiles, including long-term or rare occurrences, and its impact on morbidity and mortality. [20]

KEY COMPONENTS :

INCLUSION CRITERIA :

Inclusion criteria define the characteristics that participants must have to be eligible for a clinical trial. These may include:

1. Age: Specific age ranges, such as 18-65 years old .
2. Medical condition: Specific diseases or conditions, such as diabetes or hypertension .
3. Ethnicity: Specific ethnic groups, such as African American or Hispanic .
4. Smoking status: Smoker or non-smoker .[21]

EXCLUSION CRITERIA :

Exclusion criteria define the characteristics that would make a participant ineligible for a clinical trial. These may include:

1. Pregnancy or breastfeeding: To avoid potential harm to the foetus or baby .
2. Chronic conditions: Certain conditions, such as kidney disease or heart failure, that may interact with the treatment. [22]
3. Medications: Certain medications that may interact with the treatment .
4. Recent vaccinations: To avoid potential interference with the treatment .[23]

IMPORTANCE OF INCLUSION AND EXCLUSION CRTIERIA :

Inclusion and exclusion criteria are crucial to ensure that clinical trials are conducted safely and efficiently. These criteria help researchers:

1. Ensure participant safety: By excluding participants with certain medical conditions or medications that may interact with the treatment .
2. Increase study validity: By including participants who are representative of the population the treatment is intended .
3. Reduce bias: By excluding participants who may be biased towards a particular outcome .[24]

ENDPOINTS :

1. Primary Endpoint: The main outcome measure of the trial, used to determine the efficacy of the intervention.
2. Secondary Endpoint: Additional outcome measures that provide further information about the intervention's effects.[25]
3. Surrogate Endpoint: A measure that substitutes for a clinically meaningful endpoint, often used to accelerate trial completion. [26]

SAMPLE SIZE CALCULATION:

1. Importance of Sample Size: Adequate sample size ensures reliable estimates of treatment effects and minimizes the risk of false positives or false negatives.
2. Factors Influencing Sample Size: Effect size, variability, alpha and beta errors, and study design all impact sample size calculations.

3. Methods for Sample Size Calculation: Formula-based approaches, simulation-based methods, and software packages (e.g., SAS) are used to calculate sample size. [27]

RANDOMIZATION :

It is one of the procedures by which we allocate the interventions to different groups. Randomization ensures that all the included participants have a specified probability of being allocated to either of the groups in the intervention study. Randomization ensures that the known and particularly unknown variables are equally distributed across both groups. However, it has been highlighted that even after randomization the groups may not be similar. Thus, it is still important to compare the intervention groups at baseline in your analysis (you may want to account for some of the observed differences – if any in your analysis). By randomization, we also ensure that the allocation into different groups is not dependent on the investigator.

BLINDING :

If the participants and the investigator know about the allocation of the intervention, then it is called an "open trial. "However, many of the trials are not open – they are blinded. Blinding is useful to minimize bias in clinical trials. The investigator may blind the allocation of intervention, assessment of individuals, or data analysis. The various types of blinding were as follows:

Single-blinded trials :

In this type of trial, the patients are blinded to the intervention. However, the investigators know about the intervention given to the participants. The main disadvantage is with this design is that bias due to investigator evaluation and assessment will not be avoided in this type of design.

Double-blinded trials :

Many of the RCTs are double-blinded trials. In such a design, neither the investigator nor the participants know about the intervention allocation to the participants. This type of blinding reduces the biases due to assessment and evaluation by the investigators. [28]

ADVANCES IN CLINICAL TRIAL :

ADAPTIVE DESIGNS :

Adaptive Designs (AD's) present an alternative to convention, fixed trial designs. ADs are a type of clinical trial design in which carefully planned changes may occur during the study. A defining feature of AD trial is that changes are pre-planned (written into the study protocol) and have pre-defined rules, which allow these modifications to roll out during the trial without additional approvals, such as changes to sample size or the number of treatment arms or the allocation ratio of patients to different treatment arms , as well as early termination of the trials if an intervention is not safe, or not effective.ZXCVBN Additionally, ADs can often provide information about the effectiveness, futility, and safety of interventions earlier than fixed designs, due to an increased number of interim analyses. Earlier identification of ineffective therapies, can cut down on the overall participant burden and cost of a trial and limit exposure to unsafe interventions .[29]

We conducted systematic searches of EMBASE, PubMed, Cochrane Registry of Controlled Clinical Trials and Web of Science databases in September 2014 using phrases in English derived from descriptions of the 10 most common forms of adaptive designs: adaptive hypothesis, adaptive treatment-switching, biomarker adaptive, adaptive dose-finding, pick-the-winner/drop-the-loser, sample size re-estimation, adaptive randomization, adaptive group sequential, adaptive seamless and multiple adaptive.

Table 2: DEFINITION OF DIFFERENT TYPES OF ADAPTIVE DESIGN[30]

Type of adaptive design	Definition
Adaptive dose-finding	These trials allocate patients to multiple different treatment doses and patient responses are assessed at interim analyses. Trial design is then adapted to allocate more patients to the treatment doses of interest, reducing allocation of patients to doses that appear non-informative. These studies usually occur in early-phase research to identify doses used in subsequent studies.

Type of adaptive design	Definition
Adaptive hypothesis	A study design in which trial hypotheses are adapted in response to interim analysis results. For example, adaptive hypothesis trials could involve a preplanned shift from a single hypothesis to multiple hypotheses, preplanned switching between the null hypothesis and the alternative hypothesis or preplanned switching between the primary and secondary study endpoints.
Adaptive group sequential	In these variants on classical group sequential studies, results are analyzed at interim analyses, with prespecified options of making adaptations such as sample size re-estimation, modification/deletion/addition of treatment arms, changing study endpoints, modifying dose and/or treatment duration or adapting randomization schedules.
Adaptive randomization	A study design in which accumulating results are observed and the randomization scheme is adjusted so that patients enrolled later in the trial have a higher probability of being randomized to the treatment arm that was more effective among earlier patients in the trial.
Seamless Phase II/III	A study design that combines the objectives of the Phase II investigational stage with the Phase III efficacy or confirmatory stage into a single study protocol moving from one stage to the second stage without stopping the patient enrolment process.
Adaptive treatment-switching	A study design allowing the investigator to switch a patient's treatment from an initial assignment to an alternative treatment due to apparent lack of efficacy, disease progression or safety issues associated with the initial treatment.
Biomarker adaptive	This method allows adaptations to trial design based on interim analysis of the treatment responses of biomarkers, such as genomic markers. This design can be used to select patient populations for subsequent trials, identify the natural course of a disease, achieve early detection of a disease and/or help in developing personalized medicine.
Pick-the-winner/drop-the-loser	A study design that allows for dropping the inferior treatment group(s), modifying treatment arms and/or adding additional arms based on the review of accumulating data at interim analysis.
Sample size re-estimation	A study design using a flexible sample size adjustment or re-estimation based on interim analysis of accumulating data.
Multiple adaptive	This refers to a trial that incorporates multiple adaptive designs into a single study.

SPECAIALIZED TRIAL DESIGNS:

1.CROSSOVER DESIGNS:

In cross-over clinical trial study design, there are two groups who undergoes the same intervention/experiment at different time periods of the study. That is, each group serves as a control while the other group is undergoing the intervention/experiment. Depending on the intervention/experiment, a 'washout' period is recommended. This would help eliminate residuals effects of the intervention/experiment when the experiment group transitions to be the control group. Hence, the outcomes of the intervention/experiment will need to be reversible as this type of study design would not be possible if the subject is undergoing a surgical procedure.[31]

2.MULTIPLE ARM TRIALS:

There are two main types of multiple-arm trials. The first includes multiple dose levels or regimens of the experimental treatment all compared vs a single-control arm. In these so-called dose-response studies, it is ideal to include a zero-dose, or placebo, arm to avoid a situation in which all doses show similar activity and to establish whether any of the doses was

superior to no treatment. The second involves a single treatment arm with multiple control arms (e.g., both an active control and a placebo control arm).[32]

FUTURE DIRECTIONS:

As the landscape of clinical trials continues to evolve, several future directions are poised to transform the design and conduct of clinical trials.

1. Artificial Intelligence (AI) and Machine Learning (ML): AI and ML will play increasingly important roles in clinical trials design, from optimizing trial protocols to identifying potential participants.[33]
2. Real-World Evidence (RWE) and Pragmatic Trials: RWE and pragmatic trials will become more prominent, enabling researchers to evaluate treatments in real-world settings. [34]
3. Precision Medicine and Personalized Trials: Precision medicine and personalized trials will continue to grow, allowing researchers to tailor treatments to individual patients' needs. [35]
4. Digital Health Technologies and Mobile Health: Digital health technologies and mobile health will revolutionize clinical trials, enhancing patient engagement, data collection, and remote monitoring. [36]
5. Global Health and Low-Resource Settings: Clinical trials in global health and low-resource settings will increase, addressing the need for context-specific solutions and improving health outcomes in underserved populations. [37]

CONCLUSION:

The evolution of clinical trials design has transformed the way we evaluate new treatments, devices, and interventions. From humble beginnings to modern methodologies, clinical trials have become increasingly sophisticated, incorporating advances in statistics, technology, and regulatory frameworks. Best practices in clinical trials design, including randomization, blinding, and intention-to-treat analysis, have become essential for ensuring trial validity and reliability.

As the landscape of clinical trials continues to evolve, future directions will focus on harnessing the power of artificial intelligence, machine learning, and real-world evidence to enhance trial efficiency, effectiveness, and patient-centeredness. The integration of precision medicine, digital health technologies, and mobile health will further transform the clinical trials paradigm.

Ultimately, the goal of clinical trials design is to provide high-quality evidence that informs healthcare decisions, improves patient outcomes, and advances medical knowledge. By embracing best practices, leveraging emerging trends, and fostering collaboration among stakeholders, we can optimize clinical trials design and accelerate the development of innovative treatments that improve human health.

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