IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
Volume 3, Issue 2, January 2023
Impact Factor: 7.301

Review on Clinical Research

Praveen V. Patil, Sanjay K. Bais, Snehal Rajkumar Thombare
Fabtech College of Pharmacy, Sangola, Solapur, Maharashtra, India

Abstract: *Clinical trials are crucial to the practise of evidence-based medicine and health care reform, as demonstrated by the recent federal funding focus on comparative effectiveness research. Clinical trials have an impact on society as a whole by raising the quality of healthcare offered, in addition to having an impact on the individual patient by creating a wider range of effective therapies. Clinical trials may, however, also expose participants to unforeseen hazards, and skewed knowledge drawn from problematic clinical studies may unintentionally damage patients. A well-designed clinical trial's execution may seem simple, but it is based on meticulous procedures and oversight that adhere to fundamental ethical norms. I give an overview of the moral principles in this project.*

Keywords: Clinical trials

I. INTRODUCTION

The explosion in health care costs in the United States has recently spurred large federal investments in health care to identify the medical treatments of highest value. Specifically, $1.1 billion has been appropriated by the American Recovery and Reinvestment Act of 2009 for "comparative effectiveness" research to evaluate " clinical outcomes, effectiveness, and appropriateness of items, services, and procedures that are used to prevent, diagnose, or treat diseases, disorders, and other health conditions."

The numerous study designs can address these goals, clinical trials (and Specifically Randomized Controlled Trials [RCTs]) remain the benchmark for comparing disease interventions. And in the implementation of clinical trials involves a rigorous approach founded on scientific, statistical, ethical, and legal considerations.

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. We present key concepts as well as the dilemmas encountered in the successful design and execution of a clinical trial.

Clinical trials are scientific studies intended to assess the efficacy or safety of: drugs, medical devices, vaccines, therapeutic medical procedures, and diagnostic tests. Clinical trials it also be used to study and compare different medical approaches or assess their effectiveness in several groups of patients.

All medications and medical procedures must have been studied as part of a clinical trial before being approved by the regulatory agencies. Conducting a clinical trial is usually the final stage of a long research that began in a laboratory.

The basic principles for conducting clinical trials on human beings are based on the protection of individuals' rights and dignity of the human being regarding the application of biology and medicine. These principles are reflected in claims and agreements such as the Declaration of Helsinki and in laws such as Spanish Organic Law 15/1999 on the Protection of Personal Data.

It is fundamental that clinical trials have a proper design, that strict scientific standards prioritizing patients' protection are followed, and that high quality data are obtained, since this will later allow physicians to make relevant decisions.

It is mandatory to apply Good Clinical Practice (GCP) Guidelines to properly plan, conduct, record and communicate all clinical trials that are conducted in Spain. Prior to starting a clinical trial, it must be assessed and approved by both the Spanish Agency of Medicinal Products and a Medical Research and Ethics Committee.

1.1 The Ethical Foundation of Clinical Trials

Despite the first reported modern clinical trial described in James Lind's "A Treatise of the Scurvy" from 1753, it was not until the mid-20th century that ethical considerations in human research were addressed. In response to the criminal medical experimentation of human subjects by the Nazis during World War II, 10 basic principles of human research were formulated as the Nuremberg Code of 1949.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
Volume 3, Issue 2, January 2023
Impact Factor: 7.301

This code was later extended globally as The Declaration of Helsinki and adopted by the World Medical Association in 1964.

It is the advanced the ethical principle of "clinical equipoise," a phrase later coined in 1987 to describe the expert medical community's uncertainty regarding the comparative efficacy between treatments studied in a clinical trial.

This ethical precept guides the clinical investigator in executing comparative trials without violating the Hippocratic Oath. Further advancement of the principles of respect for persons, beneficence (to act in the best interest of the patient), and justice emerged in the 1979 Belmont Report, which was commissioned by the US government in reaction to the Tuskegee syphilis experiment.

This report applied these concepts to the processes of informed consent, assessment of risks and benefits, and equitable selection of subjects for research. Importantly, the boundaries between clinical practice and research were clarified, distinguishing activities between "physicians and their patients" from those of "investigators and their subjects." Here, research was clearly defined as "an activity designed to test a hypothesis…to develop or contribute to generalizable knowledge."

1. This is a research study (including an explanation of the purpose and duration; and the risks, benefits, and alternatives of the intervention)
2. Participation is voluntary
3. The extent to which confidentiality will be maintained
4. Contact information for questions or concerns

In 1991, the ethical principles from these seminal works were culminated into Title 45, Part 46 of the Code of Federal Regulations, titled "Protection of Human Subjects." the "Common Rule," it regulates all federally supported or conducted research, with additional protections for prisoners, pregnant women, children, neonates, and fetuses.

1.2 Overview of Trial Design

Clinical trials, in their purest form, are designed to observe outcomes of human subjects under "experimental" conditions controlled by the scientist. This is contrasted to noninterventional study designs (ie, cohort and case-control studies), in which the investigator measures but does not influence the exposure of interest.

A clinical trial design is often favored because it permits randomization of the intervention, thereby effectively removing the selection bias that results from the imbalance of unknown/immeasurable confounders. Within this inherent strength is the capacity to unveil causality in an RCT. Randomized clinical trials, however, still remain subject to limitations such as misclassification or information bias of the outcome or exposure, co-interventions (where one arm receives an additional intervention more frequently than another), and contamination (where a proportion of subjects assigned to the control arm receive the intervention outside of the study).

Execution of a robust clinical trial requires the selection of an appropriate study population. Despite all participants voluntarily consenting for the intervention, the enrolled cohort may potentially differ from the general population from which they were drawn. This type of selection bias, called "volunteer bias," may arise from such factors as study eligibility criteria, inherent subject attributes (eg, geographic distance from the study site, health status, attitudes and beliefs, education, and socioeconomic status), or subjective exclusion by the investigator because of poor anticipated enrollee compliance or overall prognosis.

The RCTs seek to achieve internal validity by enrolling a relatively homogeneous population according to predefined characteristics, narrow inclusion and exclusion criteria may limit their external validity (or "generalizability") to a broader population of patients with highly prevalent comorbidities that may not be included in the sample cohort. This theme underscores why an experimental treatment's "efficacy" (ie, a measure of the success of an intervention in an artificial setting) may not translate into its "effectiveness" (ie, a measure of its value applied in the "real world"). Attempts to improve patient recruitment and generalizability using free medical care, financial payments, and improved communication techniques are considered ethical as long as the incentives are not unduly coercive.

In order to assess the efficacy of an intervention within the context of a clinical trial, there must be deliberate control of all known confounding variables (including comorbidities), thereby requiring a homogeneous group of participants. However, the evidence provided by a well-designed and executed clinical trial will have no value if it cannot be applied to the general population. The designers of clinical trials must use subjective judgment (including clinical,

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
Volume 3, Issue 2, January 2023
Impact Factor: 7.301

epidemiological, and biostatistical reasoning) & to determine at the outset how much trade-off they are willing to make between the internal validity and generalizability of a clinical trial For a trial to adequately address the "primary question(s)" of interest, a sufficient sample size is required to have enough power to detect a potential statistical difference.

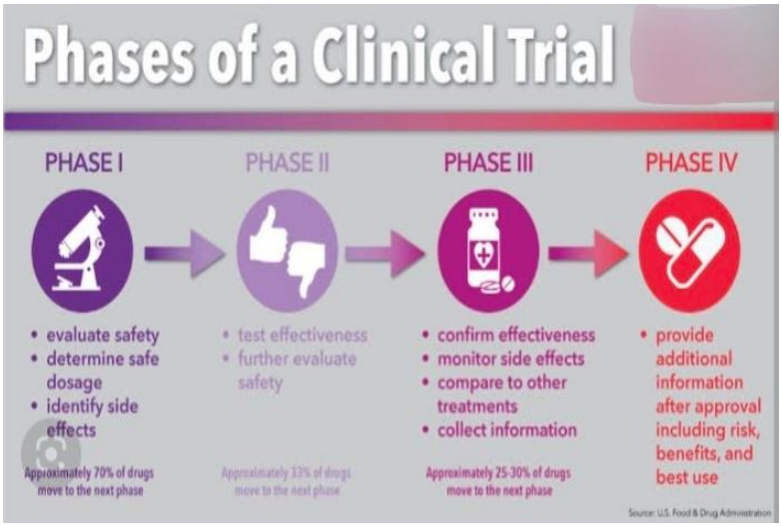
II. OVERVIEW OF DRUG DEVELOPMENT

The general road to drug development and approval has been defined and regulated by the US Food and Drug Administration (FDA) for decades. Safety has historically been its primary focus, followed by efficacy. If a drug appears promising in pre-clinical studies, a drug sponsor or sponsor-investigator can submit an investigational new drug (IND) application. This detailed proposal contains investigator qualifications and all pre-clinical drug information and data, and a request for exemption from the federal statutes that prohibit interstate transport of unapproved drugs.

After the approval, the drug is studied (phase I–III trials, described below) and if demonstrated safe and efficacious in the intended population, the drug sponsor can then submit a New Drug Application (NDA) to the FDA. After an extensive review by the FDA that often involves a recommendation by an external committee, the FDA determines whether the therapeutic can be granted an indication and marketed.

Phase IV trials, in which the safety and efficacy of the medication is assessed for the target population, may be conducted after final approval. Through the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, efforts have been made to harmonise this approval procedure throughout the United States, Europe, and Japan in order to facilitate evaluation and endorsement of foreign drug data (ICH).

2.1 Pre-Clinical, Phase I, and Phase II Trials



Pre-clinical investigations include animal studies and evaluations of drug production and purity.

Animal studies explore:

1. The drug's safety in doses equivalent to approximated human exposures,
2. Pharmacodynamics (ie, mechanisms of action, and the relationship between drug levels and clinical response), and
3. Pharmacokinetics (ie, drug absorption, distribution, metabolism, excretion, and potential drug–drug interactions).

This data must be submitted for IND approval if the drug is to be further studied in human subjects.

The FDA emphasizes "safety first," it is logical that the first of 4 stages (known as "phases") of a clinical trial is designed to test the safety and maximum tolerated dose (MTD) of a drug, human pharmacokinetics and pharmacodynamics, and drug–drug interactions.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
Volume 3, Issue 2, January 2023
Impact Factor: 7.301

These phase I trials (synonymous with "dose-escalation" or "human pharmacology" studies) are the first instance in which the new investigational agent is studied in humans, and are usually performed open label and in a small number of "healthy" and/or "diseased" volunteers.

For example, despite strong evidence that objective response rates in phase I trials of chemotherapeutic drugs is exceedingly low (as low as 2.5%), patients may still have a "therapeutic misconception" of potentially receiving a direct medical benefit from trial participation. Improvements to the process of could be help dispel some of these misconceptions while still maintaining adequate enrollment numbers.

Phase II trials, also referred to as "therapeutic exploratory" trials, are usually larger than phase I studies, and are conducted in a small number of volunteers who have the disease of interest. They are designed to test safety, pharmacokinetics, and pharmacodynamics, but may also be designed to answer questions essential to the planning of phase III trials, including determination of optimal doses, dose frequencies, administration routes, and endpoints.

In addition, they may offer preliminary evidence of drug efficacy by:

1. Comparing the study drug with "historical controls" from published case series or trials that established the efficacy of standard therapies,
2. Examining different dosing arms within the trial, or
3. Randomizing subjects to different arms (such as a control arm).

At the conclusion of the initial trial phases, a meeting between the sponsor(s), investigator(s), and FDA may occur to review the preliminary data, IND, and ascertain the viability of progressing further to a phase III trial (including plans for trial design, size, outcomes, safety concerns, analyses, data collection, and case report forms). Manufacturing concerns may also be discussed at this time.

2.2 Phase III Trials

Based on prior studies demonstrating drug safety and potential efficacy, a phase III trial (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 and/or confirm efficacy and to identify and estimate the incidence of common adverse reactions. However, given that phase III trials are usually no larger than 300 to 3000 subjects, they consequently have the statistical power to establish an adverse event rate of no less than 1 in 100 persons.

This highlights the significance of phase IV trials in identifying less-common adverse drug reactions, and is one reason why the FDA usually requires more than one phase III trial to establish drug safety and efficacy.

The most common type of phase III trials, comparative efficacy trials (often referred to as "superiority" or "placebo-controlled trials"), compare the intervention of interest with either a standard therapy.

The best-designed placebo-controlled studies, it is not uncommon to demonstrate a placebo effect, in which subjects exposed to the inert substance exhibit an unexpected improvement in outcomes when compared with historical controls. While some attribute the placebo effect to a general improvement in care imparted to subjects in a trial, others argue that those who volunteer for a study are acutely symptomatic and will naturally improve or "regress to the mean" as the trial progresses.

Equivalency trials, also known as "positive-control studies," are another form of phase III trials that are used to determine whether the experimental treatment is comparable to the selected comparator within a given margin. The design of this study nearly never includes a placebo. The intervention will be regarded as equivalent to the comparator as long as the discrepancies between them stay within the predetermined margin.

A hallmark of the phase III trial design is the balance in treatment of allocation for comparison of treatment efficacy. Implemented through

randomization, this modern clinical trial practice attempts to eliminate imbalance of confounders and/or any systematic differences (or biases) between treatment groups.

For example, in a trial with 2 arms, a block size of 4 subjects would be designated as 2 positions in arm A and 2 positions in arm B. Even though the positions would be randomly assigned within the block of 4 subjects, it would be guaranteed that, after randomization of 4 subjects, 2 subjects would be in arm A and 2 subjects would be in arm B

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
Volume 3, Issue 2, January 2023
Impact Factor: 7.301

The main drawback of applying a fixed-block allocation is that small block sizes can allow investigators to predict the treatment of the next patient, resulting in "unblinding."

For example, if a trial has a block size of 2, and the first subject in the block was randomized to treatment "A," then the investigator will know that the next subject will be randomized to "the other" treatment. Variable block sizes can help prevent this unblinding .

Table 1

Permutations of a 4-Block Randomization Scheme in a 2-Arm Study with 24 Subjects

Within-Block Assignment Group	Schedule				
	1	2	3	4	5
1	A	A	B	B	A
2	B	B	A	A	A
3	A	B	B	A	B
4	B	A	A	B	B

Permutations of a 4-Block Randomization Scheme in a 2-Arm Study with 24 Subjects. Another feature of phase III trial design is stratification, which is commonly employed in combination with randomization to further balance study arms based on prespecified characteristics (rather than size in the case of blocking).

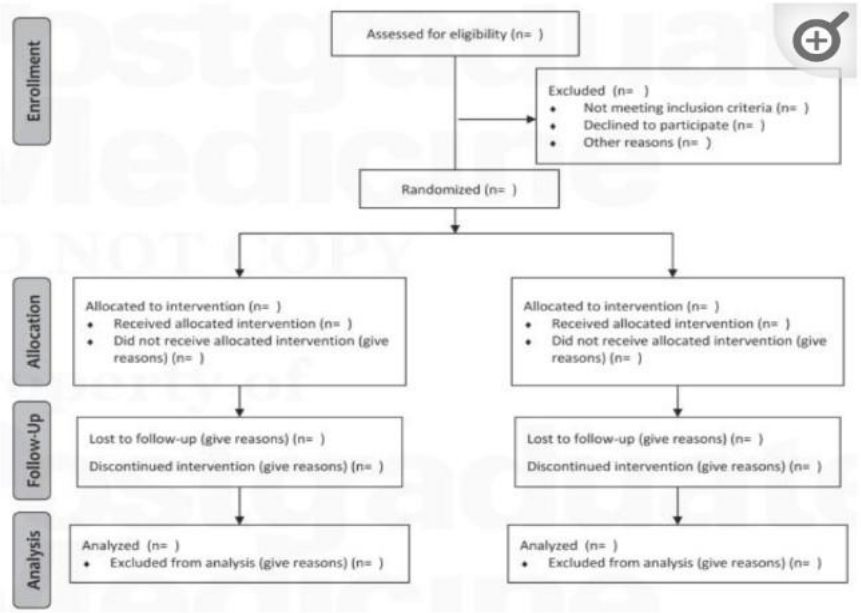
The phase III trial design dictates that the interventions be "blinded" (or masked) in an effort to minimize assessment bias of subjective outcomes. Specific blinding strategies to curtail this "information bias" include

"single blinding" (subject only),

"double blinding" (both subject and investigator), or

"triple blinding" (data analyst, subject, and investigator).

Unfortunately, not all trials can be blinded (eg, method of drug delivery cannot be blinded), and the development of established drug toxicities may lead to inadvertent unmasking and raise ethical and safety issues.



IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
Volume 3, Issue 2, January 2023
Impact Factor: 7.301

2.3 Phase IV Trials

Once a drug is approved, the FDA may require that a sponsor conduct a phase IV trial as a stipulation for drug approval, although the literature suggests that less than half of such studies are actually completed or even initiated by sponsors.

Phase IV trials, also referred to as "therapeutic use" or "post-marketing" studies, are observational studies performed on FDA-approved drugs to:

1. Identify less common adverse reactions, and
2. Evaluate cost and/or drug effectiveness in diseases, populations, or doses similar to or markedly different from the original study population.

Limitations of pre-marketing (eg, phase III) studies become apparent with the statistic that roughly 20% of drugs acquire new black box warnings post-marketing, and approximately 4% of drugs are ultimately withdrawn for safety reasons. As described by one pharmaco-epidemiologist, "this reflects a deliberate societal decision to balance delays in access to new drugs with delays in information about rare adverse reactions."

The most common criticisms of the FDA's post-marketing surveillance are:

1. The reliance on voluntary reporting of adverse events, resulting in difficulty calculating adverse event rates because of incomplete data on total events and unreliable information on the true extent of exposures;
2. The trust in drug manufacturers to collect, evaluate, and report drug safety data that may risk their financial interests; and
3. The dependence on one government body to approve a drug and then actively seek evidence that might lead to its withdrawal. Proposed solutions include the establishment of a national health data network to oversee post-marketing surveillance independent of the FDA-approval process.

General criteria for IRB approval include:

1. Risks to subjects are minimized, and are reasonable in relation to benefits;
2. Selection of subjects is equitable;
3. Informed consent is sought;
4. Sufficient provisions for data monitoring exist to maintain subjects' safety;
5. Adequate mechanisms are in place to ensure subject confidentiality; and
6. Rights and welfare of vulnerable populations are protected.

III. CONCLUSION

It is critical to comprehend the fundamental ideas involved in conducting clinical trials in order to provide patients with the most efficient and secure treatments. This fact is underscored by the media's focus on safety-based drug withdrawal, which has involved about 1.5 drugs annually since 1993. Key stakeholders may be better prepared to address future research conundrums both domestically and internationally if they understand the ethical principles and rules behind trial designs. Clinical trials that are properly planned and carried out can make a significant contribution to the national effort to increase the effectiveness and efficiency of healthcare in the United States.

REFERENCES

[1]. Craig A. Umscheid (MD, MSCE) David J. Margolis (MD, PhD, MSCE) and Craig E. Grossman (MD, PhD)

[2]. Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law. 10. Vol. 2. US Government Printing Office; Washington, DC: 1949. pp. 181–182. [Google Scholar]

[3]. World Medical Organization Declaration of Helsinki. December 7, 1996. BMJ. 1996:1448–1449. [Google Scholar]

[4]. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med. 1987;317(3):141–145. [PubMed] [Google Scholar]

[5]. Department of Health and Welfare . The Belmont report: ethical principles and guidelines for the protection of human subjects of research. OPRR Reports; Washington, DC: 1979. [PubMed] [Google Scholar]

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
Volume 3, Issue 2, January 2023
Impact Factor: 7.301

[6]. Brandt AM. Racism and research: the case of the Tuskegee Syphilis Study. Hastings Cent Rep. 1978;8(6):21–29. [PubMed] [Google Scholar]

[7]. Services DoHaH, editor. Code of Federal Regulations–The Common Rule: Protection of Human Subjects. Vol. 45. p. 2009. [Google Scholar]

[8]. Lansimies-Antikainen H, Laitinen T, Rauramaa R, Pietilä AM. Evaluation of informed consent in health research: a questionnaire survey. Scand J Caring Sci. 2010;24(1):56–64. [PubMed] [Google Scholar]

[9]. Ridpath JR, Wiese CJ, Greene SM. Looking at research consent forms through a participant-centered lens: the PRISM readability toolkit. Am J Health Promot. 2009;23(6):371–375. [PubMed] [Google Scholar]

[10]. Gravetter FJ, Forzano LAB. Research Methods for the Behavioral Sciences. 3rd ed Wadsworth Cengage Learning; Belmont, CA: 2009. [Google Scholar]