REVIEW ARTICLE

Clinical Trials: Advancing Medical Solutions for Health

Dilsar Gohil, Rajesh Maheshwari, Cyril Sajan, Krupa Joshi

Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat, India

Abstract

A clinical trial is a study conducted on human subjects to find solutions to specific medical problems. The best and quickest way to uncover treatments that are effective in individuals and to improve health is through well-conducted clinical trials. The safety and efficacy of new treatments and applications of established ones are evaluated in clinical trials. The focus of observational trials is on populations or large groups of people experiencing health problems in their everyday environments. Clinical trials, which aim to evaluate the efficacy of a treatment, are a highly specialized type of biological experiment. Clinical pharmacologists conduct phase I drug kinetics, safety, and gross effects studies on human volunteers. Phase II testing involves studying the drug's effects on a smaller group of patients to determine its pharmacokinetics, safety, and therapeutic efficiency; phase III testing involves studying hundreds more patients, primarily to determine the drug's safety and therapeutic efficacy. If this measure passes, the medicine can officially be sold. Medical professionals continue to provide feedback on the drug's safety, side effects, and effectiveness even after it has been commercialized.

Key words: Clinical trials, medical professionals, phases, volunteers

INTRODUCTION

Clinical trials are essential studies conducted on human subjects to address specific medical issues. They serve as the most efficient means to discover effective treatments and enhance health outcomes. These trials evaluate the safety and effectiveness of new treatments as well as the application of established ones. Observational trials focus on large populations experiencing health challenges in real-world settings. Clinical trials, being specialized biological experiments, involve phases of testing. Phase I studies assess drug kinetics, safety, and initial effects on human volunteers. Phase II trials examine a smaller patient group to understand pharmacokinetics, safety, and therapeutic efficacy. Phase III trials expand to include hundreds of patients, primarily to evaluate safety and therapeutic effectiveness. Successful completion of these phases allows for official approval and commercialization of the medicine. Continuous monitoring by medical professionals ensures ongoing assessment of safety, side effects, and effectiveness post-commercialization.

WHAT IS CLINICAL TRIAL?

A clinical trial is a method for assessing the quantity of data a medical test reveals about particular patients. In the assessment of patients with a disease, the function of clinical indicators is emphasized. The most effective approach for interpreting trial results is to examine the forecasting information they provide. A new test's yield should be determined using details gathered from the patient's medical record, physical exam, and standard tests.[1] For clinical trials centered on the advancement of therapies, it is vital, first, to determine whether getting involved in the research offers an acceptable probability of direct beneficial effects for subjects, and second, to explain and talk about the likelihood of direct benefit in sufficient detail to allow potential patient-subjects to make well informed choices.[2]

Address for correspondence:
Dilsar Gohil, Department of Pharmacy,
Sumandeep Vidyapeeth Deemed to be
University, Vadodara - 391 760, Gujarat, India.
E-mail: gohildilsar9624@gmail.com

Received: 02-02-2024
Revised: 17-03-2024
Accepted: 26-03-2024

Research on "clinical outcomes, productivity, and applicability of goods, commodities, or solutions, and procedures used for the avoidance, detection, and management of ailments and other health conditions." Clinical investigations are still the best way to evaluate illness therapies. Clinical trials involve a strict intellectual, arithmetic ethical and legal strategy. Health-care practitioners must understand clinical trial tenets to work with patients as well as the pharmaceutical industry to find the safest, most effective, and most cost-efficient treatments. To plan and conduct a clinical study, one must understand the key concepts and challenges.[3]

Clinical trial design with patient and public involvement (PPI) is a comprehensive study. Involving patients and the public in the planning of clinical trials can be useful but requires resources, planning, education, adaptability, and a period. Reporting deficiencies for potential bias, quality of research, and conflict of interest must be addressed. To promote PPI along with health literacy, we must address these issues and improve distribution strategies.

To promote research, patient and public engagement (PPI) design is now required. However, PPI reporting is not uniform, making it hard to identify within study reports. Clinical trials should benefit from unified documentation of PPI design, conduct, evaluation, and conclusion. Best practice for PPI in clinical trial design highlights what has been discovered as well as reported about PPI in clinical trials; identifies the context, techniques, or procedures that promote PPI and influence the procedure of research, results, and propagation of results; and encourages the adoption of successful approaches to improve PPI to reduce the expenses for resources that may result from ineffective PPI.

Patients and the public can help design clinical trials, but it takes time, resources, planning, education, and adaptability. Potential bias, quality of studies, and conflict of interest reporting deficiencies must be addressed. To promote PPI along with health literacy, we have to tackle these issues and improve distribution tactics.[4]

A BRIEF OVERVIEW OF THE DEVELOPMENT OF CLINICAL TRIALS

In 1747, Lind examined 12 scurvy patients and their reactions to various treatments. The largest recovery was seen in those who ate vitamin C-rich oranges and lemons. Through the 1800s, comparative research examined how drugs and vaccines treated smallpox, diphtheria, and cholera. The National Institutes of Health were formed in 1887 to fund the identification of illnesses, early detection, and treatment studies by the federal government. The ability to organize data, utilize analytic statistical tools, uncover novel and efficient treatment drugs, and improve clinical and surgical practices influenced clinical investigation.[5]

The 1900s' literature concentrated on viral disease prevention and treatment. With the British Medical Research Council's (MRC) first placebo-controlled randomized clinical trial, the structure of clinical trials became more rational. The first trial to randomly allocate patients to both control and experimental groups was this 1948 streptomycin trial for tuberculosis.[6] Clinical research was revolutionized by intentional randomization between an intervention and a control group. It indicated that clinical scientists understood that assigning patients to therapy groups could bias information and invalidate results.[7]

It also revealed that doctors realized clinical studies should be well-designed scientific assessments that use established methodologies to eliminate investigator bias, design errors, and subjective interpretations of treatment results. Clinical trials now depend on four elements of the British MRC's streptomycin study. First, the MRC trial randomly assigned medication after the patient was admitted, preventing the researchers' knowledge of the patient's care from affecting their decision to participate. Second, trial participants had similar clinical characteristics. These two factors ensured the impartial allocation of similar patients to groups receiving treatment, allowing researchers to make more valid and convincing findings about the drugs under study. There was an emphasis on objective documentation of therapy outcomes. Ethics were considered before the trial. These essential ideas are still applicable despite advances in research study designs and data analysis. Since WWII, medical research has relied on the prospectively randomized control clinical trial. Two variables have improved clinical research. Science creates new medical treatments. Today, patients choose medicines and take part in medical ethics.[8]

Peto *et al*. detailed the planning and analysis of modern clinical studies. An efficient trial must address a highly concentrated question or set of questions, use an objective

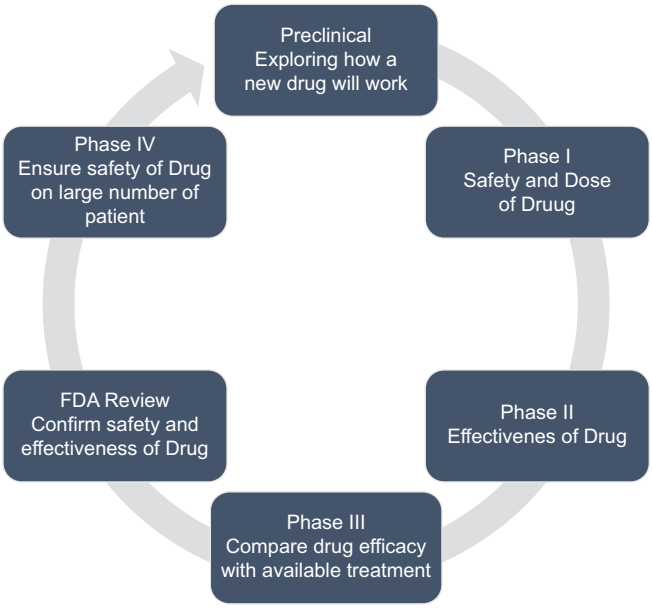

Figure 1: Phases of clinical trial

and possible method for obtaining an acceptable answer, involve investigators who have valuable clinical care as well as methodology expertise, and be conducted over a suitable period to draw precise inferences about controlling disease and overall survival.[9] It must include a clearly documented protocol that provides a particular plan for proceeding with the study that can be easily understood by all involved investigators since rigorous adherence to the procedure is crucial.[10]

PHASES OF CLINICAL TRIAL

A medication takes years to create. After laboratory testing, drugs are evaluated in humans. Clinical trials are separated into phases I, II, III, and IV. Clinical trials have different goals for each step. Phase I trials demonstrate safety; phase II trials evaluate efficacy; phase III trials compare the drug's efficacy to conventional therapy; and phase IV trials evaluate general hazards and benefits once the drug is licensed. Phases are explained below. Participants increase with each medication development phase. Risky or inefficient drugs will not make it through all four phases.[11]

The authors have created this Figure 1.

Phase I

Phase I clinical trials are modest, uncontrolled, sequential investigations involving human volunteers to identify a drug's MTD. Statistics have been neglected in phase I clinical trials because they are non-randomized, small, and hypothesis-free. Over the past 50 years, most medical trial statistical analysis has focused on large randomized phase III trials.[12]

Due to the severe adverse effects of cytotoxic medicines used to treat cancer, phase I clinical trials are especially significant in this field. Myelosuppression, immunological suppression, nausea, vomiting, anorexia, baldness, and diarrhea.[13]

Cytotoxic medications have negative effects, yet some malignancies are deadly and effective treatments are rare. Phase I cancer trial patients often have advanced tumors and may be on their last chance for survival. Participating in such a trial may give patients optimism that the experimental treatment will treat their cancer, but few will benefit. Some investigators have proposed that volunteers derive happiness from having an understanding that they are helping researchers and more effective therapies even if they do not benefit.[12] However, sociological research suggests that charitable drives play a limited and insignificant role in phase I trial participation.[14]

Due to the seriousness of the problems related to cytotoxic agents and the impact, they may have on a volunteer's quality of life, moral issues require that such trials be efficient to gather the most data with a few patients and protect volunteers from highly toxic dose levels. Accurately determining the MTD is crucial because it will be used in phase II trials. Passing on a dose under the genuine MTD may risk potentially beneficial medicine in subsequent phase trials. In later-phase trials, passing on too large a dose puts patients in danger of obtaining a highly hazardous dose. Thus, strong science is essential to balancing personal and societal ethics in therapeutic studies.[15]

Phase II

Phase II trials determine if a treatment shows enough promise to warrant a definitive phase III trial. Toxicology, biomarkers, loco regional control, distant metastases, and QOL are often assessed. Except in cases where a definite phase III study is not possible, phase II trial results should not influence the practice of medicine. Phase II trials usually have tens or hundreds of participants. One-sided type I error probabilities of 0.05–0.20 and power of at least 80% are normal in phase II trials. Disease response is the recommended primary goal for single-arm phase trials, especially with single cytotoxic drugs. In randomized trials, survival without progression and freedom from disease measure disease progression and survival. In phase II trials, overall survival is usually the primary objective for disorders with poor prognoses. Radiation therapy trials can focus on loco regional control. The primary objective in phase II no inferiority trials is usually the most substantial advantage for patients (e.g., toxicity and QOL). Prefer controlled phase II trials. Single-arm designs are suitable for trials of novel drugs with promise of action, rare illnesses, a lack of established therapies, salvage settings, or no adequate historical controls. However, a slight increase in modern detection rates compared to historical rates can raise the likelihood of a false positive.[16]

Nonrandomized trial

Single-arm trials

Eligible patients undergo the novel treatment in single-arm studies with one stage, and the main outcome analysis is performed solely at the end of the study. No protocol-specified intermediate futility or efficacy evaluations are included. However, a phase II trial should limit patient exposure to inefficient or hazardous medicines. Thus, phase II trials generally include an interim futility assessment to determine if the new medication is unlikely to be recommended for further study.[17]

Noncomparative trials

Patients are assigned to two or more experimental arms in noncomparative randomized trials (NCRTs). This design lacks a contemporaneous control arm. These designs are similar to "selection designs," which study the arm with the greatest response rate.[18] This randomized phase II-phase III approach is particularly useful for trials with time-to-event ends, illnesses with ambiguous natural histories, and biomarker-guided designs. "Randomized phase II screening trials" was the

inaugural term for short, randomized phase II trials to gather no definitive data on an experimental regimen versus a standard therapy.[19] NCRTs compare each experimental arm to historical controls using information from patients or a baseline. NCRTs mimic several single-arm trials. Thus, they share single-arm trials' drawbacks. NCRTs are powered to assess each experimental arm with historic controls; hence, they are not designed to statistically compare experiment arms.[20]

Comparative trials

Randomization balances known and unknown prognostic variables across treatment arms. It also supports causal conclusions. Controlled randomized trials are considered the "gold standard" for establishing a signal of treatment effectiveness in phase II trials before moving on to a conclusive phase III trial.[21] Instead of randomizing a varied cohort of participants to treatment groups, some writers argue that phase II studies should choose individuals more likely to benefit from therapy. Biomarker-enrichment strategies that involve randomization can alleviate these difficulties.[22,23]

Phase III

Phase II clinical studies are exploratory and help prepare for phase III, which is confirmatory. Phase II is usually smaller than phase III, and the trial failure rate is 60% and 40% for phases II and III, respectively, indicating that this habit may not be effective. Low sample sizes generally have low success possibilities. We examine sample size issues in a drug research project, including phase II and phase III sample of samples.[24]

Phase III clinical trials can be used to launch novel therapy programs, making them the most likely to change practice. Before being opened at a cancer center, practically all non-industry-sponsored phase III clinical trials in the US are established and activated through the NCI cooperative group method because of their complexity and accrual needs. For clarity, we use "activate" as a reference to the release of an accepted protocol by a team working together to the oncology community and "open" to indicate when the study protocol has obtained local site Institutional Review Board (IRB) approval and has finished all other tasks needed for the trial to be made accessible for patient accumulation at that site.[25]

A phase III trial's clinical success is best demonstrated by a positive effect on a clinically significant endpoint, which directly assesses a patient's symptoms, function, or survival.[26] At one extreme, a novel medicine is developed with a single candidate biomarker and solid biological evidence that marker-negative individuals will not benefit. Phase III clinical studies that develop a predictive descriptor genome-wide and validate it internally are the opposite.[27]

It provides novel, safe, and effective medications. Phase II trials fail 70% of the time. As "exploratory," "proof of mechanism," and "proof of concept" experiments in individuals, early-phase trials are likely to fail. Surprising is the 50% failure rate of "confirmatory" Phase III experiments. Early-phase trials should qualify a therapeutic program for Phase III testing, but few do.[28]

Phase IV

Due to phase I-III trials' small sample numbers, short length, and rigorous inclusion and exclusion criteria, a drug's safety profile at regulatory approval is often inadequate.[29] All new medications must undergo extensive premarketing research.[30,31] The Food and Drug Administration Amendment Act of 2007 empowered the FDA to demand post-marketing clinical trials to address medication safety issues. Phase IV studies assess drug safety in the real world, unlike premarketing phase I-III trials. This may help ensure or improve drug safety.[32] Modern phase IV clinical trials and their ability to increase pharmacovigilance knowledge remain unknown.[33]

PMS studies are phase IV studies, although not all phase IV studies are PMS studies. Phase IV is vital to medication development. In particular, an observational, non-interventional trial in a naturalistic context that supports pre-marketing randomized controlled trial (RCT) efficacy data No matter how many patients are investigated premarketing in a controlled environment; the true safety record of a medicine is only described by ongoing surveillance through an unplanned adverse event tracking system and a post-marketing monitoring or nonintervention study. Prevalent patterns of practice can yield leads that could lead to additional RCT examination of a new indication or regulatory action.[34] PMS studies the effectiveness and toxicity of a medication under conditions similar to clinical use to identify specific conditions of benefit or hazard and assess the drug's overall effect, both interest and actual, on the circumstances for which it is prescribed. Both short-term and long-term effects should be monitored and identified.[35]

Goals are:

1. To offer post-marketing statistics on the general population's long-term responses to medication therapy
2. To report delayed drug reactions
3. To simultaneously analyze favorable and harmful reactions that might be used for cost-benefit evaluations,
4. To offer information on outpatient and inpatient medication responses
5. To give information on prescription and over-the-counter pharmaceuticals,
6. To provide data on drug interactions and single drug effects, and
7. To ensure security and confidentiality to safeguard patients, counselors, and organizations.[36]

Drug development's "Phase IV" is used for this. Phases I–III of drug development are premarketing and the authors say they leave critical concerns unaddressed. After the FDA

approves a new drug application (NDA) and the molecule is widely used in clinical practice, Phase IV should be applied to all drug studies, according to the authors. Phase IV studies can overcome pre-marketing evaluation's shortcomings in four major areas and may be crucial for medication development.

Areas include:

1. Adverse reactions, Pre-marketing studies will miss various forms of adverse reactions. These include delayed adverse effects that do not look like medication reactions.
2. Efficacy Concerns some may remain unsolved in marketing. For instance, medications may reduce illness recurrence, progression, or consequences over time. Due to clinical testing's, tendency to compare a single prototype molecule against an array of other medicines, pre marketing studies lack comparable data.
3. Utilization Data: After commercialization, certain drug use characteristics may be investigated for the 1st time. Phase IV studies could investigate novel uses or activities in more selected groups. In phase IV, drug use could be assessed for appropriateness, compatibility, overuse, and misuse.
4. Cost or risk/benefit ratio: Phase IV allows the 1st time to determine society's complete influence on advantages, dangers, and costs.[37]

ETHICAL AND REGULATORY CONCERN REGARDING CLINICAL TRIALS

Clinical trials in poor nations have increased due to the worldwide expansion of clinical research. Legal and ethical rules must be strengthened to protect participants in studies as clinical trials grow globally. Over a decade ago, observers remarked that developing nations were conducting experiments without respect for global ethical standards. Therefore, internationalization of clinical trials can be beneficial as it gives subjects access to new therapies, but it also requires discussion and surveillance of ethical issues related to guaranteeing the integrity, welfare, and safety of research participants and to bioethical principles such as independence, beneficence, kindness, justice, and equality.[38]

GOOD CLINICAL PRACTICE (GCP)

GCP principles are raised in the 2005 Document of the Americas. The clinical research team's experts' qualifications are among these. To carry out their tasks as clinical study participants and experts, they must have the necessary training, experience, and education.[39] Regulatory agency inspections found that the staff was not trained in GCP and the research protocol, notwithstanding improvements in compliance. In its 2012 report, the European Medicines Agency found 11% of GCP inspections to have deficiencies in team training and competency. Health Canada (Canada's regulatory agency) has 8.9% of study teams with poor qualifications, education, and training.[40]

Lack of written clinical procedures and GCP training for study coordinators and center staff is one example of a weakness. In addition, the lead investigator's sub-investigators and nurses' study activities were not documented.[41] The Brazilian Health Surveillance Agency (Anvisa) inspections of clinical practices found 12%, 15%, and 27% of deviations due to a lack of protocol, GCP, or both protocol and GCP training.[42]

It may be tempting to conduct clinical trials in impoverished nations; however, considerations, including preserving study participants' rights, must be considered. Legal and ethical rules must be strengthened to protect research subjects as clinical studies grow globally. More than a century ago, several observers remarked that research was being conducted in underdeveloped countries without regard to the 1947 Nuremburg Code and 1964 Helsinki Declaration.[43]

INTERNATIONAL HARMONIZATION IN GCP: QUALITY ASSURANCE OF CLINICAL TRIALS

The FDA, the US regulatory agency, publishes a list of researchers who have been banned from drug clinical studies. In these examples, the exclusion is due to improper behavior in US clinical trials. The FDA-disqualified physician cannot perform drug clinical studies. Studies have been faked and FDA information withheld.[44] Serious frauds include fabricating all or part of the study's data, presenting false or altered data to get results that support the study's initial hypotheses, and stealing ideas from different original studies. Investigators' desire to share their work and industry pressure to quickly publish results for the commercialization of products can lead to study fraud. Benefits can collide with researchers' industry pressure.[45]

In one study of Canadian clinical researchers, 37% reported having been involved in conflicts of financial interest, mostly linked to recruitment capacity (getting financial advantages for speedy participant recruitment). About 24% acknowledged financial conflicts of interest related to the study. Industry support for research was present in 72% of financial conflicts.[46]

DECLARATION OF HELSINKI

As is generally known, the Helsinki Declaration was born from physicians' international efforts to establish medical ethics after World War II. The WMA's initial attempt was to amend the Hippocratic Oath with the document known as the Declaration of Geneva (1948), which concentrated on physicians' ethical duties, to patients.[47,48] After that, the WMA developed ethical

guidelines for doctors conducting human studies in medicine. It was created as a reaction to the International War Crimes Tribunal's indictment of several famous German physicians for their brutal medical experiments on prisoners.[49,50] The Nüremberg Court's judgment included the Nüremberg Code, which outlined medical experimentation's ethical standards. The Declaration has changed throughout time to reflect the growing realization of the need for accurate consent in medical practice, not simply research. New technological as well as scientific breakthroughs were also addressed.[51] Williams said the Declaration's evolution balanced public and individual interests while emphasizing that individual interests are essential and cannot be overruled by society or science. "Therapeutic" and "non-therapeutic" studies were eliminated in the 2000 Declaration version. The Declaration also barred the use of placebos where an existing medicine was available and required researchers to seek public benefit in their studies.[52]

International research ethics debates have developed in recent decades. Due to budget constraints and fairness, the argument centered on placebo use and post-trial treatment. This previous changes demonstrate that the statement addresses current medical research problems. The declaration must reflect the new requirements. The Declaration of Helsinki came from human research subject abuse. Research supervision has risen, although some populations have been underrepresented. Thus, the Declaration of Helsinki becomes increasingly authoritative for human medical research.[53]

Low-resource economies benefit from the updated Declaration of Helsinki because it clearly covers crucial issues, including post-trial access to medicines and care for individuals in low-resource situations. In low-resource countries, towns may be used to test expensive and inaccessible projects. Accessible interventions are required under the new declaration. Research can improve therapy in low-resource conditions. The new statement acknowledges research's importance in improving care by allowing experimental solutions in limited-resource settings. With patient consent and professional help, the 2013 Declaration of Helsinki advises utilizing untested therapies.[54]

Medical research in developing nations has been debated internationally. Because they addressed pertinent difficulties, the Council for International Organizations of Medical Sciences guidelines 7 were preferred to the Declaration of Helsinki in resource-limited contexts. The new Declaration of Helsinki addresses a number of issues that affect research in developing nations, such as the need to include underrepresented groups in research, the importance of efficient ethics boards, post-trial accessibility to care, the use of untested actions, and strengthening informed consent. The statement addressed these concerns to recognize limited-resource situations' importance in research data collection. Low-resource stakeholders should value the declaration. This Declaration of Helsinki empowers research ethics committees, funders, and participants by emphasizing fairness.[55]

The 2013 Declaration of Helsinki includes major changes after 50 years and seven amendments. By adding subsections and changing the format, the updated declaration resolves difficulties.[56]

THE CLINICAL RESEARCH TEAM

Staff is crucial to a research program, but it is also costly. Nurses and data administrators each spend 30% of the time and effort needed to perform clinical research, whereas physicians spend 9%.[57]

The authors have created this Figure 2.

Task delegation for research

Clinical trials are overseen by a study site's lead investigator, who might delegate research activities to qualified employees. Matching people to jobs ensures that program resources are spent efficiently and that personnel like and are challenged by their work.[58]

Due to differences in expertise and licensure, it can be difficult to assign research team tasks. Clinical Research Associate (CRAs), study nurses, information managers, and research coordinators may work on a research team. Depending on a program's organizational structure, everyone may have different tasks. The staff screens potential study candidates, determines eligibility, coordinates the patient calendar, prepares documents for IRBs, files amendments, submits safety data, educates patients, obtains informed consent, and assesses potential adverse events. If resources allow, an administrator or coordinator can oversee assurance of quality, staffing, spending, and site audits.[59]

After delegating work, many sites employ a delegate log to track which staff member is responsible for each research assignment. Because trial staff roles vary, each research project should have a delegation log. Staff training courses should be documented on the site. Training logs can be classified into (1) new research team member training and (2) ongoing research team training.[60] SOPs that cover training requirements help document and sustain the process. Since clinical research training is not typically included in health-related or nursing programs, it is recommended that CRAs and research nurses pursue specialist certification in addition to fulfilling the minimum requirements for basic research training.[61,62]

Data management in clinical trials

Clinical Data Management (CDM) is a crucial phase in clinical research that generates superior, trustworthy, and valid statistical data from clinical trials. This drastically reduces manufacturing and promotional time. CDM team members participate in all clinical trial phases. They need

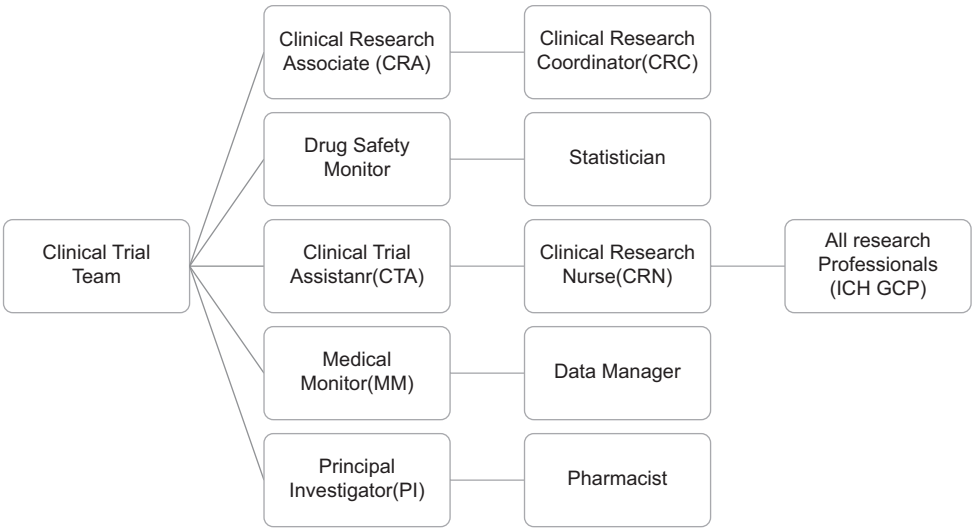

Figure 2: Clinical trial team

expertise in processes to sustain CDM process quality. At regular times during a study, CDM operations such as Case Report Form (CRF) development, CRF commenting, information establishing, data entry, confirmation of data, contradiction administration, health-care coding, data collection, and information locking are examined for quality. To meet regulatory criteria and commercialize products faster, CDM standards must be improved. CDM can address these objectives with regulatory-compliant data management technology. In addition, companies must submit data digitally. CDM experts should create data quality, satisfy standards, and respond to continuously evolving technologies.[63]

CDM involves collecting, cleansing, and managing subject data in accordance with regulations. CDM processes aim to acquire the most data for evaluation and minimize errors and data shortages.[64] To guarantee that data are comprehensive, reliable, and handled correctly, guidelines are used. Software solutions that keep an audit trail and make errors in information easier to identify and resolve have made this possible. CDM can manage large trials and assure the accuracy of information even in challenging trials thanks to sophisticated advancements.[65]

Study document review and completion

Like a clinical trial, the CDM process starts with its conclusion. The approach is developed with the output in mind. The CDM procedure creates a free of errors, valid, and reliable database to answer an investigation question in a clinical study. To achieve this goal, the CDM process begins before the study design is finalized.[66,67]

For clarity and uniformity, an information system designer reviews the protocol. The CDM will determine the information items to be gathered and their frequency based on the visit plan during this evaluation. The CDM team first designs a CRF to translate protocol-specific actions into data. Data fields must be well defined and consistent. CRFs should indicate data types. Study researchers should get the CRF and CRF Completion Guidelines for error-free data collection. CRF annotated name variables using SDTMIG or internal protocols.[68]

DESIGNING DATABASE

Clinical software systems called databases help CDMs manage various investigations.[69] Such instruments comply with regulations and are straightforward to use. The safety of data is ensured by system validation, which evaluates system requirements, user needs, and compliance with regulations before deployment. The database defines study parameters, including goals, times of examinations, researchers, sites, and patients, and CRF designs are built for data entry. These entry fields are evaluated using dummy data before genuine data gathering.[70]

Data collection

Paper CRFs are used to collect data, which is entered into the computer system in-house. The investigator completes these CRFs on paper entered into the computer system in-house. The investigator completes these CRFs on paper. The researcher or designate will log in to the CDM system and submit data at the location in the e-CRF-based CDM. Mistakes are less likely, and inconsistencies are resolved quickly in e-CRF. Drug manufacturers are using e-CRF (remote data entry) to speed up the development of medicines.

Risk factor monitoring and data input

The CRA checks the CRF for accuracy and returns it to the CDM team. The CDM team will monitor CRFs. To prevent data loss, missing pages and unintelligible data are manually recorded in CRFs. Insufficient or unreadable data is clarified

by the investigator. Data entry follows the DMP's rules. Only paper CRFs from sites apply. Data is usually entered twice by two operators.[71] By discovering mistakes in transcription and inconsistencies resulting from illegible data, the subsequent pass entry helps verify and reconcile. Compared with just one data entry, double-entering information creates a cleaner database. Double data entry has been demonstrated to improve paper CRF uniformity and reduce mistake rates.[72]

CDM roles and responsibilities

Each member of a CDM team has a specific role. A life science degree and computer skills are the minimal requirements for CDM team members. Ideally, medical coders are medical graduates. Medical coders are also paramedical graduates. Every CDM team needs certain roles. Essential CDM team duties are listed below:

- Database administrator,
- Database programmer/designer,
- Medical coder,
- Clinical data coordinator,
- Quality control associate.

The data manager is responsible for monitoring the CDM process. The data manager creates the DMP, reviews CDM processes, and reviews all CDM-related internal papers. The information manager also manages team access to databases. CRF commentary, research database creation, and change checks for accuracy of data are done by the database programmer or designer. Data entry windows and modifications using dummy data are likewise his or her responsibility. Medical history, co-illnesses, complications, and concurrent medicines will be coded by the healthcare coder. The clinical data coordinator creates the DVP, dispute leadership, and CRF filling procedures. Clinical data coordinators create CDM checklists, guidelines, and other documentation. Quality control monitors and verifies data entry.[73]

CLINICAL RESEARCH: WHAT IS ETHICAL?

Many consider medical studies ethical with informed permission. Ethical clinical study conduct does not require informed permission. Criteria that comprehensively define a cohesive structure for assessing clinical research study ethics rely on the essential philosophy behind significant numbers, statements, and other publications pertinent to studies involving human subjects.[74]

Benefit for the enhancements of health or understanding must be derived from the study; scientific legitimacy the research must be scientifically rigorous.[75] Adequate subject choice for scientific goals, not risk or privilege, and the possibility for the allocation of risks and benefits ought to decide the groups chosen as locations for the study and the criteria for inclusion for each of the individuals.[76] Beneficial risk and benefit ratio within the setting of typical clinical procedures.[77] Self-sufficient evaluation for unaffiliated humans have to evaluate the study's results and endorse, amend, or terminate it; informed consent of individuals should be updated about the research and provide their voluntary consent; and consideration for the subject areas of the class subjects ought to have their confidentiality safeguarded, the opportunity to withdraw, and their well-being monitored. Clinical research is ethical if all these conditions are met. Clinical research must adapt these parameters to health, financial, social, and technological conditions, but they are universal.[78]

RCTs have surpassed clinical judgment, case studies, and observational research as medicine's gold standard. RCTs also become vital to the regulatory process for new therapeutics to enter the drug industry. As research issues get more complex, clinical trials must balance ethical and epistemological norms. In this review, the author will explore some of the most relevant ethical concerns concerning RCTs, keeping an eye on recent controversy and oncological research in specific, in this review.[79]

ETHICAL CONCERNS

Participation with informed consent

In current times, consent to a therapeutic or study program must have three parts. It must be voluntary, capable, and knowledgeable. Although each of the three elements of informed authorization has issues in their practical use, the concept is most often questioned since it's hard to define what's enough knowledge for permission.[80] Data that renders consent valid involves knowing the risks and advantages of the treatment(s) individuals may receive, recognizing the procedures that they might go through, including blinding and randomization in RCTs, recognizing that research involvement is voluntary, and comprehending the objective of the study. At every point, defining the right amount of information is tough. In medical care, consent with knowledge is required for diagnostics or medical procedures. In complex treatments, the MD may struggle to explain a diagnosis or curative technique, its risks, and its potential advantages to the individual receiving therapy.[81]

The issue is further complicated in the field of medicine because the goal is not to help individuals. The trial's main goal is not to provide medicinal advantages to participants. The therapeutic fallacy occurs when participants believe the study's goal is to determine the most effective therapy for them.[82] Some physicians believe that "a dominating ethical view" encourages treatment misperception because scientific researchers are also clinicians.[83]

Deception and the use of placebo

Patients and scientists' treatment expectations may affect therapeutic progress in unforeseen ways. Thus, a placebo may be given to control group patients in a scientific trial of a new intervention. Placebos are indistinguishable from experimental treatments but lack the active principle. Deception is the first issue with placebos. The placebo effect only works if placebo patients think they are getting a real treatment. However, it is debatable whether placebo-controlled trials deceive people. When they give their consent to the trial, participants are advised that they will not be told if they are taking an active drug or a placebo.[84]

However, the risk of injury from placebos is a major concern. People without active therapy risk worsening their diseases, dying, or experiencing increased discomfort. In such cases, placebos are immoral since they injure individuals for the good of other parties the scientists finishing the research. In some circumstances, the mock-controlled design can be changed to examine both the effect of placebo and the actual therapy response in a single group of individuals, avoiding leaving certain in-trial individuals untreated. Crossover trials are so named because participants switch between the placebo and therapy arms at predefined times.[85]

Randomization and blinding

RCTs must randomize and blindfold subjects. These two evidentiary devices are needed to rule out any particularly apparent distortions of the trial result due to investigator or patient involvement. However, randomization and blinding may interfere with study participants' interests. Randomization and blinding prevent patients from making condition-specific therapy decisions.[86] Equipoise, a cognitive condition of indifference to two therapies, can alleviate this ethical dilemma, according to modern ethical theory. If the medical profession is in disagreement, physicians are in "honest professional disagreement" on which treatment is best.[87] Randomization, a "fair bet" among equally important outcomes, does not hurt those who participate.[88]

Despite its ethical effectiveness, equipoise has detractors. A clinical question's equipoise conditions must be identified.[89] Whose indifference or matching is morally relevant is also clear. Based on the field of science's existing understanding, the current prevailing idea appears to be the most reasonable, but alternative options may also be valid. Even for some illnesses, patient equilibrium should be just as important since we should not anticipate an individual to be neutral between, say, an intrusive surgical treatment and an oral medication treatment.[90]

Despite these issues, equipoise remains a viable ethical model for deciding clinical study ethics, and ethical committees in research hospitals utilize it to approve fresh studies. To conclude, medical scientists and statistical experts have sought an analytical answer to reduce the likelihood of patients receiving less effective treatment. Unequal assignment (i.e., randomization with rates other than 50–50) or adaptable assignment (where allocation prices vary with trial outcomes, favoring the most successful treatment) have been suggested as well as used to achieve this goal. Due to the difficulties of rationalizing enrolling patients in the quasi-preferred arm, such scientific approaches cause greater moral issues than they resolve.[15]

Targeting agents: Ethical consideration

Targeted agents differ from conventional anticancer medications in that they work selectively. When patients with the same type of tumor but different molecular lesions are subjected to a focused compound, their reactions can vary drastically, affecting not just the extent but also the course of the treatment effect. This is important for drug trials because the targeted agent's beneficial impact is often limited to a small subset of initially eligible participants, and the subset often cannot be identified before the study.[91] The ethical difficulties surrounding targeted therapy testing appear to stem from differing evidence standards. How does the evidence needed to establish that a tailored therapy is effective differ from that needed to evaluate traditional medicines? This epistemological point must be addressed to qualify and maybe solve the ethical difficulties described above. As philosopher of medicine John Worrall has stated, no educated view of ethical concerns can be accepted without first having a full understanding of the evidential-epistemological individuals.[92]

Clinical trial management

Trial management is essential for research studies of any size or sophistication. Trials fail since apprenticeship-based approaches have not been recorded, assessed, or disseminated to guide new trialists. Trialists have redefined trial administration over the past 30 years. Standard trial procedures and comprehensive evaluation methodologies are needed to boost the successful, timely delivery of significant clinical trials to benefit patients.

We recommend that donors, trialists, trial managers, and other stakeholders meet with opinion leaders to talk about and debate trial management techniques to establish an accepted norm and guideline for clinical study management. We also advise that professional journal editors examine the significance of how well a study is done and need trial management strategies in publications submitted for publication. Trial management's absence of uniform methodology and training will hurt future studies and medical treatment.[93]

When do trials succeed?

Success depends on active trial management. Clinicians must be familiar with trial procedures in order to recruit participants.

One-on-one instruction, collaboration, and online films and teleconferences can do this. Trial team members must organize national and international speeches and conversations to emphasize the trial's importance. A trial manager's and teams largest problem is maintaining an individual interface with a cooperative team of physicians, whether they number 7 or 700. However, doing so will result in a more coherent study.[94]

As defined by project management, a clinical trial is similar to other corporate projects. The following are features:

- A specific goal to change
- A team
- A deadline
- Determined resources for its goal
- Required tasks every project involves a series of steps to achieve results. Steps 1–5 are:
    1. Initiating
    2. Planning
    3. Executing
    4. Managing
    5. Reporting.[95]

Collaboration

Good evidence that the clinical question being addressed is in equipoise is vital, but it is just part of the problem. Clinicians and nurses are likely to recruit subjects, so the query should be relevant to them. The majority of challenges need a cohesive group to succeed. Inclusion is the goal of a team or network. From procedure creation to result dissemination, participation and discussion will support this. All trials must be extensively marketed. This plan will include a recognizable name and/or symbol and an expert image. Collaboration between disciplines has been shown to be more successful.[96] For major trials, this is going to be a team of professionals with site representation. For single-center and shorter research, the team may comprise a few compatible people.[97]

The duties of researchers and volunteers

Ensuring recruitment methods operate according to usual practices minimizes investigator and participant work. Site visits and conversations with recruitment staff will make trial recruitment a regular practice. Clinical progression and form completion should determine question order. Data collected as "free text" increases the workload and danger of misinterpretation, but is sometimes unavoidable. Edwards' recent essay on questionnaire design and administration gives a theoretical framework but acknowledge the need for further examination.[98]

Effective systems

A trial, especially a major one, needs solid computerized systems and processes to oversee every aspect of its daily operation. A dependable system that monitors recruiting, selection, inventory oversight, organizing data, data cleansing, and centralized information monitoring and produces meaningful reports should be built. Effective trial management produces high-quality data. Computers help speed up data validation and quality control, but they must be flexible to meet researcher and trial needs. Researchers and data management teams can reduce work by using digital data capture technologies that reduce data input steps. However, form development and training must be done in advance if trialists want to use electronic data capture. Clinical trial laws require computer system developers to follow data layout, testing, and verification standards.[99]

Trial recruitment efficiency

There is minimal research to inform recruitment tactics, but a trial's success or failure depends on whether it recruits the prespecified number of people to accurately answer the question. Monetary incentives, an additional questionnaire on invitation, and treatment details on the permission form were beneficial.[100] However, individual experimental interventions are difficult to generalize. The authors found that most interventions' effects on recruitment could not be predicted based on this evidence.[101]

Publication and distribution

The project development and management strategy also addresses how credit for the trial will be distributed. If the findings are not shared and applied, the study is pointless. Trial results can be extensively disseminated through medical publications, online journals, trial registrations, systematic reviews, and conference presentations. Each investigator in a multicenter experiment can disseminate and present locally under an established policy. Trial results should be published regardless of the outcome, and not doing so is scientific misconduct.[102]

Knowledge, skills, and experience

Every trial team member must have the right education, training, and experience, according to the EU Clinical Trials Directive 2001. Since there is no specialized training in trial management and no recognized qualification to establish a trial manager's education, it is difficult for any trial manager to comply with this law.[103]

Digital clinical trials: The future's vision

Over the past decade, electronic devices have changed practically every area of our lives, including how we interact, purchase, and read. Digital health technologies may be able to alter clinical trials if they receive adequate funding and regulation. Simply digitizing current research methods will

not be enough to accomplish this. Instead, the clinical study experience should be rethought and reengineered around the participant, not the research facility. Some trials may be virtual, but most will require a mix of online and clinical site-based activity.[104]

Clinical trials provide an independent examination of suggested health and health-care breakthroughs and comparative options for treatment, diagnosis, and prevention. Trials should be situated in clinical practice and include people who will use the novel medicines or delivery methods to guide clinical decision-making. Unfortunately, the medical study infrastructure is slowly evolving, making clinical trials logistically difficult and expensive. It is clear the clinical trial system needs improvement.[105]

Many interested parties turn down clinical trials due to time and travel requirements. Clinicians are further discouraged by the many repeated activities needed in the existing clinical trials industry, many of which are superfluous if digital data streams are fully utilized. Due to limited enrollment, medical choices are often based on results from an unrealistically uniform community.[106] Most clinical trials take roughly twice as long to enroll, with half of the study sites enrolling no or few individuals. This is caused by the lack of varied volunteers.[107] This and other factors add to clinical trial expenses, which can reach hundreds of millions of dollars.[108]

As data quality and types advance, electronic health records and claims data from routine care combined with actual-world signals from cellphones, wearables, implants, and at-home sensor technology will enable remote, ongoing surveillance of participants, eliminating most travel to a clinical site. These modifications will also enable greater frequency and real-time participant follow-up, eliminating the need for in-clinic exams. Innovative sensors, such as constant glucose monitoring, can provide new data to refine phenotypes.[109]

This kind of connectivity also reduces regional barriers to participation and allows volunteers to receive individual and overall study data throughout the study, building a true scientific partnership. Digital trials may truly collaborate with participants and allow patients to develop and conduct clinical trials.[110]

In digital world participant recruiting, enrollment, and afterward, which generate money for research facilities, are a major obstacle to digital clinical trials. Many corporate and educational study groups will encounter the same challenges that several firms have had over the last decade as they deal with digital disruption to drive transformation. However, compared to particular photography, travel, retailing, and numerous other sectors driven by customer preference, research supply almost entirely depends on clinical trial funders, whether grant critics or health-care leaders, who tend to promote conventional wisdom rather than drive innovation.

Patients and professionals agree that decision-making needs better and faster evidence. The clinical researcher community, funding organizations, and policymakers must work together to stimulate creativity in methodology and establish a digital clinical study industry. Market forces pushed digital change in many other industries.

PHARMACIST IN CLINICAL TRIALS

Pharmacists participate in research and clinical trials. We store investigational medicinal products (IMPs) in the fridge or at a controlled room temperature. The temperature is monitored and reported regularly. The pharmacist must also maintain IMP supply and dispensation. In addition to the informed consent form and patient information leaflet, patients are counseled about IMP use. To determine treatment compliance, patients' IMP returns are counted and logged. Pharmacists will also prepare and administer injectable IMPs to meet trial requirements. Oncology pharmacists manage clinical trials and conduct research to improve patient outcomes after receiving chemotherapy or other supporting pharmaceuticals such as anti-emetics, blood growth factor injections, etc. Pharmacists do drug utilization evaluations (DUEs). These initiatives encourage rational drug use among our patients. In essence, studying patient drug use and physician prescribing patterns because pharmacists check medication use, DUEs are sometimes called drug audits. Pharmacists also conduct observational surveys to assess patients' and physicians' drug views. Our patient services are improved using survey results. NCC's cancer pharmacy is conducting two surveys. They examine patients' usage of alternative and complementary therapies and oral anti-cancer drug safety. Pharmacy students trained in research routinely survey patients.[111]

DISCUSSION

In summary, we have learned about the ethics of clinical trials, the role of the FDA, the responsibilities of the investigator and the institution, the different phases of clinical trials, the different types of clinical trials, and the experimental methods that are used in each phase. The goal of a clinical trial is to determine whether or not a treatment is safe and effective (how well it functions under ideal conditions). The trial is explained to volunteers who satisfy certain criteria, such as having the ailment being examined. This informed consent process usually involves a written form to document the issues and the volunteer's consent, and it should include outlining the random assignment of therapy as well as the hazards and possible advantages of the experiment. The process of creating and approving a novel medicine is fraught with numerous regulatory restrictions. The creation of a novel medicine cannot occur without the use of clinical trials. Well-designed, well-controlled, and carefully supervised clinical studies with healthy volunteers and/or patients who consent

to participate are required before a new treatment can be made available. Roche is dedicated to protecting patient safety and privacy, in addition to conducting high-quality studies, for the benefit of all parties involved in the healthcare system. Proper documentation of processes and outcomes is required at all times. From a regulatory standpoint, the research does not exist if it is not documented. A NDA is submitted once all necessary clinical trials for a newly developed drug have been finished, as well as any concomitant nonclinical investigations. Regulations for INDs offer specific instructions for both content and structure. Before drafting an NDA, sponsors typically consult with the FDA to discuss the document's intended purpose and structure.

CONCLUSION

Our exploration has provided a comprehensive understanding of the multifaceted world of clinical trials. We've delved into the ethical considerations that underpin the conduct of these trials, emphasizing the paramount importance of protecting the rights and well-being of trial participants. The pivotal role of the FDA in overseeing the drug approval process has been highlighted, showcasing the stringent regulatory framework that governs the development and testing of new treatments. We've also examined the responsibilities of investigators and institutions, stressing the need for meticulous planning, execution, and documentation throughout the trial process. Understanding the different phases and types of clinical trials, from early-stage safety assessments to large-scale efficacy studies, is crucial for ensuring the validity and reliability of trial results. Roche's commitment to upholding the highest standards of patient safety, privacy, and scientific integrity has been underscored, reflecting the broader ethos of pharmaceutical companies in the healthcare landscape. Ultimately, the journey from experimental concept to market-ready treatment hinges on adherence to regulatory requirements, with the submission of a New Drug Application marking a pivotal milestone in the translation of research findings into tangible medical advancements.

REFERENCES

1. Harrell FE Jr., Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. JAMA 1982;247:2543-6.
2. King NM. Defining and describing benefit appropriately in clinical trials. Hum Exp Res 2017;12:383-94.
3. Umscheid CA, Margolis DJ, Grossman CE. Key concepts of clinical trials: A narrative review. Postgrad Med 2011;123:194-204.
4. Price A, Albarqouni L, Kirkpatrick J, Clarke M, Liew SM, Roberts N, *et al.* Patient and public involvement in the design of clinical trials: An overview of systematic reviews. J Eval Clin Pract 2018;24:240-53.
5. Dowling H. The emergence of the cooperative clinical trial. Tram Stud Co11 Physicians Phila 1975;43:20-9.
6. Medical Research Council Investigation. Streptomycin treatment of tuberculosis. Br Med J 1948;2:769-82.
7. Hill AB. Suspended judgment. Memories of the British Streptomycin Trial in Tuberculosis. The first randomized clinical trial. Control Clin Trials 1990;11:77-9.
8. Doll R. Clinical trials: Retrospect and prospect. Stat Med 1982;1:337-44.
9. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer 1976;34:585-612.
10. Cancer Therapy Evaluation Program: Investigator's Handbook. Bethesda, MD: National Cancer Institute; 1986.
11. Sedgwick P. Phases of clinical trials. BMJ 2011;343:d6068.
12. Rosenberger WF, Haines LM. Competing designs for phase I clinical trials: A review. Stat Med 2002;21:2757-70.
13. Schacter L, Birkhofer M, Carter S, Canetta R, Hellmann S, Onetto N, *et al*. Anticancer drugs. In: O'Grady J, Joubert PH, editors. Handbook of Phase I=II Clinical Trials. CRC Press: Boca Raton; 1997. p. 523-34.
14. Daugherty C, Ratain MJ, Grochowski E, Stocking C, Kodish E, Mick R, *et al.* Perceptions of cancer patients and their physicians involved in phase I trials. J Clin Oncol 1995;13:1062-72.
15. Palmer CR, Rosenberger WF. Ethics and practice: Alternative designs for phase III randomized clinical trials. Control Clin Trials 1999;20:172-86.
16. Torres-Saavedra PA, Winter KA. An overview of phase 2 clinical trial designs. Int J Radiat Oncol Biol Phys 2022;112:22-9.
17. Stallard N, Whitehead J, Todd S, Whitehead A. Stopping rules for phase II studies. Br J Clin Pharmacol 2001;51:523-9.
18. Rubinstein L. Phase II design: History and evolution. Chin Clin Oncol 2014;3:48.
19. Rubinstein LV, Korn EL, Freidlin B, Hunsberger S, Ivy SP, Smith MA. Design issues of randomized phase II trials and a proposal for phase II screening trials. J Clin Oncol 2005;23:7199-206.
20. Yom SS, Torres-Saavedra P, Caudell JJ, Waldron JN, Gillison ML, Xia P, *et al.* Reduced-dose radiation therapy for HPV-associated oropharyngeal carcinoma (NRG Oncology HN002). J Clin Oncol 2021;39:956-65.
21. Grayling MJ, Dimairo M, Mander AP, Jaki TF. A review of perspectives on the use of randomization in phase II oncology Trials. J Natl Cancer Inst 2019;111:1255-62.
22. Freidlin B, Korn EL. Biomarker enrichment strategies: Matching trial design to biomarker credentials. Nat Rev Clin Oncol 2014;11:81-90.
23. Freidlin B, McShane LM, Polley MY, Korn EL. Randomized phase II trial designs with biomarkers. J Clin Oncol 2012;30:3304-9.
24. De Martini D. Allocating the sample size in Phase II and III trials to optimize success probability. Epidemiol Biostat Public Health 2014;11:4.
25. Dilts DM, Cheng SK, Crites JS, Sandler AB, Doroshow JH.

Phase III clinical trial development: A process of chutes and ladders. Clin Cancer Res 2010;16:5381-9.
26. Raghu G, Collard HR, Anstrom KJ, Flaherty KR, Fleming TR, King TE Jr., *et al.* Idiopathic pulmonary fibrosis: Clinically meaningful primary endpoints in phase 3 clinical trials. Am J Respir Crit Care Med 2012;185:1044-8.
27. Simon R. Clinical trials for predictive medicine. Stat Med 2012;31:3031-40.
28. Pretorius S. Phase III trial failures: Costly, but preventable. Appl Clin Trials 2016;25:36.
29. Gale EA. Post-marketing studies of new insulins: Sales or science? BMJ 2012;344:e3974.
30. Englev E, Petersen KP. ICH-GCP Guideline: Quality assurance of clinical trials. Status and perspectives. Ugeskr Laeger 2003;165:1659-62.
31. Dixon JR Jr. The international conference on harmonization good clinical practice guideline. Qual Assur 1999;6:65-74.
32. Glasser SP, Salas M, Delzell E. Importance and challenges of studying marketed drugs: What is a phase IV study? Common clinical research designs, registries, and self-reporting systems. J Clin Pharmacol 2007;47:1074-86.
33. Schmidt LG, Grohmann R, Helmchen H, Langscheid-Schmidt K, Müller-Oerlinghausen B, Poser W, *et al.* Adverse drug reactions. An epidemiological study at psychiatric hospitals. Acta Psychiatr Scand 1984;70:77-89.
34. Suvarna V. Phase IV of drug development. Perspect Clin Res 2010;1:57-60.
35. Remington RD. Recommendations. In: Allan FN, editor. Assessing Drug Reactions--Adverse and Beneficial. Philosophy and Technology of Drug Assessment. Vol. 7. Washington, DC: The Interdisciplinary Communications Associates, Inc.; 1976. p. 141-50.
36. Slone D, Shapiro S, Miettinen OS, Finkle WD, Stolley PD. Drug evaluation after marketing. Ann Intern Med 1979;90:257-61.
37. Blackwell B, Stolley PD, Buncher R, Klimt CR, Temple R, Venn D, *et al.* Panel 4: Phase IV investigations. Clin Pharmacol Ther 1975;18:653-6.
38. da Silva RE, Amato AA, Guilhem DB, Novaes MR. Globalization of clinical trials: Ethical and regulatory implications. Int J Clin Trials 2016;3:1-8.
39. Organização Panamericana da Saúde. Organização Mundial da Saúde. Rede Panamericana Para Harmonização da Regulamentação Farmacêutica Boas Práticas Clínicas: Documento das Américas. United States: Organização Panamericana da Saúde; 2005.
40. European Medicines Agency (EMA). Annual Report of the Good Clinical Practices Inspectors Working Group; 2012.
41. Health Canada. Summary Report of Inspections of Clinical Trials Conducted from April 2004 to March 2011. Available from: https://www.hc-sc.gc.ca/dhp-mps/compli conform/clini-pract-prat/report-rapport/2004-2011-eng.php#a5314 [Last accessed on 2020 May 02].
42. Agência Nacional de Vigilância Sanitária. Ministério da Saúde. Inspeções em Boas Práticas Clínicas. Pasta Pública. Brasil: Nacional de Vigilância Sanitária; 2014.
43. Annas GJ. Globalized clinical trials and informed consent. N Engl J Med 2009;360:2050-3.
44. Food and Drug Administration - FDA. Inspections, Compliance, Enforcement, and Criminal Investigations. Clinical Investigators - Disqualification Proceedings. Available from: https://www.fda.gov/iceci/enforcementactions/ucm321308.htm14 [Last accessed on 2020 May 02].
45. Sepúlveda AQ. Perspectivas Éticas de la publicación Biomédica. In: Novaes G, Quezada FL, editores. Monografías de Acta Bioethica. Ética y Farmacia. Una Perspectiva Latinoamericana. Chile: Centro Interdisciplinario de Estudios en BioéticaUniversidad de Chile–OPAS/OMS: N 2, OPAS/OMS; 2009. p. 301-10.
46. Rochon PA, Sekeres M, Hoey J, Lexchin J, Ferris LE, Moher D, *et al.* Investigator experiences with financial conflicts of interest in clinical trials. Trials 2011;12:9.
47. Declaration of Geneva. Physician's Oath: Adopted by the General Assembly of World Medical Association at Geneva Switzerland; 1948. Available from: https://www.cirp.org/library/ethics/geneva [Last accessed on 2009 Apr 10].
48. Lederer SE. Research without borders: The origins of the declaration of Helsinki. In: Schmidt U, Frewer A, editors. History and Theory of Human Experimentation. Stuttgart, Germany: Franz Steiner Verlag; 2007. p. 145-64.
49. Annas GJ, Grodin MA, editors. The Nazi doctors and the Nuremberg Code: Human Rights in Human Experimentation. New York: Oxford University Press; 1992.
50. Mitscherlich AM. The Nuremberg code (1947). In: Doctors of infamy: The Story of the Nazi Medical Crimes. New York: Schuman; 1949. p. 23-5.
51. Goodyear MD, Krleza-Jeric K, Lemmens T. The declaration of Helsinki. BMJ 2007;335:624-5.
52. Williams JR. The Declaration of Helsinki and public health. Bull World Health Organ 2008;86:650-2.
53. Sherwin S. Women in clinical studies: A feminist view. In: Mastriani A, Faden R, Federman D, editors. Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies. Institute of Medicine; 1994.
54. Mandava A, Pace C, Campbell B, Emanuel E, Grady C. The quality of informed consent: Mapping the landscape. A review of empirical data from developing and developed countries. J Med Ethics 2012;38:356-65.
55. Council for International Organizations of Medical Sciences. International Ethical Guidelines for Biomedical Research Involving Human Subjects; 2002. Available from: https://www.cioms.ch/images/stories/CIOMS/guidelines/guidelines_nov_2002_blurb.htm [Last accessed on 2013 Oct 13].
56. Ndebele P. The Declaration of Helsinki, 50 years later. JAMA 2013;310:2145-6.
57. Emanuel EJ, Schnipper LE, Kamin DY, Levinson J, Lichter AS. The costs of conducting clinical research. J Clin Oncol 2003;21:4145-50.

58. Baer AR, Devine S, Beardmore CD, Catalano R. Clinical investigator responsibilities. J Oncol Pract 2011;7:124-8.
59. Zon R. Role of the Oncology Team. In: Presented at the International Clinical Trials Workshop. Cairo, Egypt; 2011. Available from: https://www.semco-oncology.info/6-semco_download.html
60. Society of Clinical Research Associates. Available from: https://www.socra.org [Last accessed on 2022 Aug 05].
61. Association of Clinical Research Professionals. Available from: https://www.acrpnet.org [Last accessed on 2022 Aug 12].
62. American Society of Clinical Oncology: A Multidisciplinary Approach to Clinical Trials: The Role of Surgeons. Available from: https://www.asco.org/ASCOv2/researchresources/researchactivities/clinicaltrialresources/clinicaltrialvide [Last accessed on 2022 Sep 03].
63. Krishnankutty B, Bellary S, Kumar NB, Moodahadu LS. Data management in clinical research: An overview. Indian J Pharmacol 2012;44:168-72.
64. Gerritsen MG, Sartorius OE, vd Veen FM, Meester GT. Data management in multi-center clinical trials and the role of a nation-wide computer network. A 5 year evaluation. Proc Annu Symp Comput Appl Med Care 1993;92:659-62.
65. Lu Z, Su J. Clinical data management: Current status, challenges, and future directions from industry perspectives. Open Access J Clin Trials 2010;2:93-105.
66. CFR - Code of Federal Regulations Title 21 Internet Maryland: Food and Drug Administration; 2010. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=11.10 [Last accessed on 2011 Mar 01].
67. Study Data Tabulation Model Internet Texas: Clinical Data Interchange Standards Consortium; c2011. Available from: https://www.cdisc.org/sdtm [Last accessed on 2011 Mar 01].
68. CDASH Internet Texas: Clinical Data Interchange Standards Consortium; c2011. Available from: https://www.cdisc.org/cdash [Last accessed on 2011 Mar 01].
69. Fegan GW, Lang TA. Could an open-source clinical trial data-management system be what we have all been looking for? PLoS Med 2008;5:e6.
70. Kuchinke W, Ohmann C, Yang Q, Salas N, Lauritsen J, Gueyffier F, *et al.* Heterogeneity prevails: The state of clinical trial data management in Europe - results of a survey of ECRIN centres. Trials 2010;11:79.
71. Cummings J, Masten J. Customized dual data entry for computerized data analysis. Qual Assur 1994;3:300-3.
72. Reynolds-Haertle RA, McBride R. Single vs. double data entry in CAST. Control Clin Trials 1992;13:487-94.
73. Ottevanger PB, Therasse P, van de Velde C, Bernier J, van Krieken H, Grol R, *et al.* Quality assurance in clinical trials. Crit Rev Oncol Hematol 2003;47:213-35.
74. Childress JF. The place of autonomy in bioethics. Hastings Cent Rep 1990;20:12-7.
75. Beauchamp TL. Methods and principles in biomedical ethics. J Med Ethics 2003;29:269-74.
76. Vanderpool HY. The ethics of research involving human subjects: Facing the 21st century.
77. Freedman B. Scientific value and validity as ethical requirements for research: A proposed explication. IRB 1987;9:7-10.
78. Truog RD, Robinson W, Randolph A, Morris A. Is informed consent always necessary for randomized, controlled trials? N Engl J Med 1999;340:804-7.
79. Nardini C. The ethics of clinical trials. Ecancermedicalscience 2014;8:387.
80. Berg JW, Appelbaum P, Lidz C. Informed Consent: Legal Theory and Clinical Practice. 2nd ed. New York: Oxford University Press; 2001.
81. Herz DA, Looman JE, Lewis SK. Informed consent: Is it a myth? Neurosurgery 1992;30:453-8.
82. Appelbaum PS, Lidz CW. The therapeutic misconception. In: Emanuel EJ, Grady CC, Crouch RA, Lie RK, Miller FG, Wendler DD, editor. The Oxford Textbook of Clinical Research Ethics. Oxford: Oxford University Press; 2008. p. 633-43.
83. Miller FG, Brody H. A critique of clinical equipoise: Therapeutic misconception in the ethics of clinical trials. Hastings Cent Rep 2003;33:19-28.
84. Wendler D, Miller FG. Deception in the pursuit of science. Arch Intern Med 2004;164:597-600.
85. Deng C, Hanna K, Bril V, Dalakas MC, Donofrio P, van Doorn PA, *et al*. Challenges of clinical trial design when there is lack of clinical equipoise: Use of a response conditional crossover design. J Neurol 2012;259:348-52.
86. Hellman S, Hellman DS. Of mice but not men: Problems of the randomized clinical trial. N Engl J Med 1991;324:1585-9.
87. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med 1987;317:141-5.
88. Edwards SJ, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J. Ethical issues in the design and conduct of randomised controlled trials. Health Technol Assess 1998;2:1-132.
89. Sackett DL. Why randomized controlled trials fail but needn't: 1. Failure to gain "coal-face" commitment and to use the uncertainty principle. CMAJ 2000;162:1311-4.
90. Lilford RJ. Ethics of clinical trials from a Bayesian and decision analytic perspective: Whose equipoise is it anyway? BMJ 2003;326:980-1.
91. Wistuba II, Gelovani JG, Jacoby JJ, Davis SE, Herbst RS. Methodological and practical challenges for personalized cancer therapies. Nat Rev Clin Oncol 2012;8:135-41.
92. Worrall J. Evidence and ethics in medicine. Perspect Biol Med 2008;51:418-31.
93. Farrell B, Kenyon S, Shakur H. Managing clinical trials. Trials 2010;11:1-6.
94. Farrell B, Kenyon S. On behalf of the UK Trial Managers' Network: A Guide to Efficient Trial Management. Available from: https://www.tmn.ac.uk/guide.htm [Last accessed on 2022 Nov 16].
95. Project Management Institute: A Guide to the Project

Management Body of Knowledge; 1996. Available from: https://www.unipi.gr/akad_tmhm/biom_dioik_tech/files/pmbok.pdf [Last accessed on 2022 Nov 29].
96. Fry A, Mortimer K, Ramsay L. Clinical research and the culture of collaboration. Aust J Adv Nurs 1994;11:18-25.
97. Bammer G. Enhancing research collaborations: Three key management challenges. Res Policy 2008;37:875-87.
98. Edwards P. Questionnaires in clinical trials: Guidelines for optimal design and administration. Trials 2010;11:2. Available from: https://www.fda.com/csv/index.html [Last accessed on 2022 Dec 05].
99. Mapstone J, Elbourne D, Roberts I. Strategies to Improve Recruitment to Research Studies. (Cochrane Methodology Review). The Cochrane Library Chichester. UK: John Wiley & Sons Ltd.; 2004. p. 2.
100. Rendell JM, Merritt RD, Geddes JR. A Cochrane review on incentives and disincentives to participation by clinicians in trials. Cochrane Database Syst Rev 2007;18:MR000021.
101. Chalmers I. Underreporting research is scientific misconduct. JAMA 1990;263:1405-8.
102. European Commission: EU Clinical Trials Directive; 2001. Available from: https://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf [Last accessed on 2022 Dec 16].
103. Steinhubl SR, Wolff-Hughes DL, Nilsen W, Iturriaga E, Califf RM. Digital clinical trials: Creating a vision for the future. NPJ Digit Med 2019;2:126.
104. Anderson A, Borfitz D, Getz K. Global public attitudes about clinical research and patient experiences with clinical trials. JAMA Netw Open 2018;1:e182969.
105. Oh SS, Galanter J, Thakur N, Pino-Yanes M, Barcelo NE, White MJ, *et al.* Diversity in clinical and biomedical research: A promise yet to be fulfilled. PLoS Med 2015;12:e1001918.
106. Getz K. The Cost of Clinical Trial Delays; 2015. Available from: https://www.ctti-clinicaltrials.org/files/pgct-session5.1-getz.pdf [Last accessed on 2020 May 19].
107. Moore TJ, Zhang H, Anderson G, Alexander GC. Estimated costs of pivotal trials for novel therapeutic agents approved by the US Food and drug administration, 2015-2016. JAMA Intern Med 2018;178:1451-7.
108. Hall H, Perelman D, Breschi A, Limcaoco P, Kellogg R, McLaughlin T, *et al.* Glucotypes reveal new patterns of glucose dysregulation. PLoS Biol 2018;16:e2005143.
109. Lewis D. History and perspective on DIY closed looping. J Diabetes Sci Technol 2019;13:790-3.
110. Wong DR, Bhattacharya S, Butte AJ. Prototype of running clinical trials in an untrustworthy environment using blockchain. Nat Commun 2019;10:917.
111. Pharmacist Role in Clinical Trial. Available from: https://www.nccs.com.sg/pbcation/tomorrow/mar 08/pharmacy [Last accessed on 2023 Jan 05].

Source of Support: Nil. **Conflicts of Interest:** None declared.