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CLINICAL TRIALS PRINCIPLES, APPLICATION AND CONTRIBUTION IN DRUG DEVELOPMENT

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ABSTRACT

Clinical trials of recent has received a lot of funding on comparative effectiveness research that has raised the importance of clinical trials the development and practice of evidence-based medicine and health care reform. Clinical trial is a very planned experiment designed to assess the efficacy of a treatment in man, by comparing the outcomes in a group of patients treated with the test treatment with those observed in a comparable group of patients receiving a control treatment, where both patients in both groups are enrolled, treated and followed over the same time period. The impact of clinical trials not only extends to the individual patient by establishing a broader selection of effective therapies, but also to society as a whole by improving the value of health care provided. Clinical trials also have the potential to present unknown risks to their participants, and biased knowledge derived from flawed clinical trials may lead to an unpredicted harm to patients. Although conducting a well-designed clinical trial may appear simple, it is based on rigorous methodology and oversight, governed by key ethical principles. This review aims at providing an overview of clinical trials, its ethical foundations, trial design, trial oversight, and the process of obtaining approval of a therapeutic agent, from its pre-clinical phase to post-marketing surveillance. With a more understanding of the key principles in designing and implementing clinical trials, health care providers can partner with the pharmaceutical industry and regulatory bodies to effectively compare medical therapies and thereby meeting one of the essential goals of health care reform.

KEYWORDS: clinical trials, drug development; clinical trials, phase 0 to phase IV trial; randomized controlled trial.

INTRODUCTION

Clinical trials are experiments or observations done in clinical research. Such prospective biomedical or behavioral research studies on human participants are designed to answer specific questions about biomedical or behavioral interventions, including new treatments (such as novel vaccines, drugs, dietary choices, dietary supplement and medical devices), and known interventions that needs further study and comparison.[1,2] Clinical trials can generate data on dosage, safety and efficacy.[3] They are conducted only after they have received health authority/ethics committee approval in the country where approval of the therapy is sought. These authorities are responsible for validating the risk/benefit ratio of the study trial, and their approval does not mean that the therapy is safe or effective, only that the trial may be conducted. Depending on product type and clinical development stage, investigators initially enroll volunteers or patients into small pilot studies, and subsequently conduct larger scale comparative studies.[4] Clinical trials can vary in size and cost, and they can involve a single research centre or multiple centres, in one country or in multiple countries. Clinical study design is focused on ensuring the scientific validity and reproducibility of the results.[5]

Costs for clinical trials can range into the billions of dollars per approved drug.[2,6] The sponsor may be a state, organization or a pharmaceutical, biotechnology or medical device companies.[3,7] Certain functions necessary to the trial, such as monitoring and laboratory-based work, may be managed by an outsourced partner, such as a contract research organization or a central laboratory.[2,8] Only 10% of all drugs started in human clinical trials become approved drugs.

Clinical Trials of drugs/ therapeutic interventions

Some clinical trials involve healthy subjects with no pre-existing medical conditions. Other clinical trials are concern with people with specific health conditions, who are willing to participate in an experimental treatment.[9] Pilot experiment are conducted to gain an insights on the design of the clinical trial to follow. There are two goals to testing medical treatments: to learn whether they work well enough, called "efficacy" or "effectiveness"; and to learn whether they are safe enough, called "safety".[4,10] Neither is an absolute criterion; both safety and efficacy are evaluated relative to how the treatment is intended to be used, what other treatments are available, and the severity of the disease or condition.[4,8] The benefits must outweigh the risks.[11] For example, many drugs for treatment of cancer (narrow therapeutic window) have severe side effects that would not be acceptable for an over-the-counter pain medication, yet the cancer drugs have been approved since they are used under a physician's care and are used for a life-threatening condition.[5,12] Pharmaceutical companies are well organized in terms of planning and partitioning of their clinical research and development platform. This organization for good clinical research is done by therapeutic area to facilitate priority and intervention in the research and development needs. This therapeutic area is shown in figure 1.

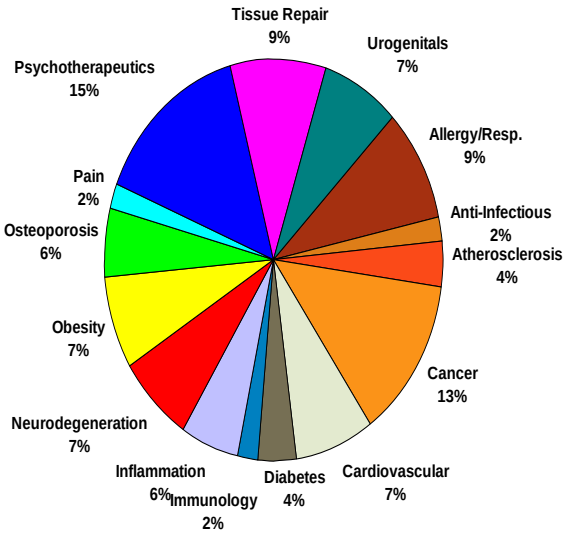

Figure 1: Schematic illustration of therapeutic diseases area in a standard drug discovery Pharmaceutical Company.[5]

In a developed country like the US, the elderly constitutes 14% of the population, while they consume over one-third of drugs.[7,13] People over 55 years of age are often excluded from clinical trials because their greater health issues and drug use complicate data interpretation, and also because they have different physiological capacity than younger people.[2,14] Children and people with unrelated medical conditions are also frequently excluded from trials.[8] Pregnant women are often excluded due to potential risks to the fetus.[15] The sponsor designs studies trial in coordination with a panel of expert clinical investigators, alternative or existing treatments to compare to the new drug and what type(s) of patients might benefit from the study. If the sponsor cannot obtain enough test subjects at one location, investigators at other locations can be recruited to join the study.[15]

During the clinical trial, investigators recruit subjects with the predetermined characteristics, administer the treatment(s) and collect data on the subjects' health for a defined period of time.[3,16] Data include measurements such as vital signs, concentration of the study drug in the blood or tissues, changes to symptoms, and whether improvement or worsening of the condition targeted by the study drug occurs. The researchers send the data to the trial sponsor, who then analyzes the pooled data using statistical tests.[17] Examples of clinical trial goals include assessing the safety and relative effectiveness of a medication or device: on a specific kind of patient, at varying dosages, for a new indication, evaluation for improved efficacy in treating a condition as compared to the standard therapy for that condition, evaluation of the study drug or device relative to two or more already approved/common interventions for that condition.[2,7,18]

While most clinical trials test one alternative to the novel intervention, some expand to three or four and may include a placebo. Except for small, single-location trials, the design and objectives are specified in a document called a clinical trial protocol.[19] The protocol is the trial's "operating manual" and ensures all researchers perform the trial in the same way on similar subjects and that the data is comparable across all subjects. As a trial is designed to test hypotheses and rigorously monitor and assess outcomes, and it can be seen as an application of the scientific method, specifically the experimental step.[15,20-21] The most common clinical trials evaluate new pharmaceutical products, medical devices, biologics, psychological therapies, or other interventions. Clinical trials may be required before a national regulatory authority[9] and approves marketing of the innovation.[14]

Clinical Trials of Medical devices

Just like drugs, manufacturers of medical devices in developed countries and mostly in the United States are required to conduct clinical trials for premarket approval [10, 22]. Medical device trials may compare a new device to an established therapy, or may compare similar devices to each other. An example observed in the field of vascular surgery is the Open versus Endovascular Repair (OVER trial) for the treatment of abdominal aortic aneurysm[23], which compared the older open aortic repair technique to the newer endovascular aneurysm device.[11,24] Other example includes clinical trials on mechanical devices used in the management of adult female urinary incontinence.[12,25] Similarly, to drugs, medical or surgical procedures may be subjected

to clinical trials[26], such as case-controlled studies for surgical interventions.[14,27]

Historical overview of clinical trials

The principles behind clinical trials dates back in the ancient times and has been illustrated by the Book of Daniel chapter 1, verses 12 through 15, for instance, describes a planned experiment with both baseline and follow-up observations of two groups who either partook of, or did not partake of, "the King's meat" over a trial period of ten days. Persian physician Avicenna, in The Canon of Medicine (1025) gave similar advice for determining the efficacy of medical drugs and substances.[15] Edward Jenner vaccinating James Phipps, a boy of eight, on 14 May 1796. Jenner failed to use a control group. Although early medical experimentation was performed often, the use of a control group to provide an accurate comparison for the demonstration of the intervention's efficacy was generally lacking.[28] For example, Lady Mary Wortley Montagu, who campaigned for the introduction of inoculation (then called variolation) to prevent smallpox, arranged for seven prisoners who had been sentenced to death to undergo variolation in exchange for their life. Although they survived and did not contract smallpox, there was no control group to assess whether this result was due to the inoculation or some other factor. Similar experiments performed by Edward Jenner over his smallpox vaccine were equally conceptually flawed.[29]

The first proper clinical trial was conducted by the physician James Lind.[16] The disease scurvy, now known to be caused by a vitamin C deficiency, had terrible effects on the welfare of the crew of long-distance ocean voyages. In 1740, the catastrophic result of Anson's cirmnavigation attracted much attention in Europe. Out of 1900 men, he conducted his study,1400 had died, most of them allegedly from having contracted scurvy.[30] John Woodall, an English military surgeon of the British East India Company, had recommended the consumption of citrus fruit (it has an antiscorbutic effect) from the 17th century, but there was not globally widespread.[18,31] James Lind therefore made some advancement in conducting the first systematic clinical trial in 1747.[32] He included a dietary supplement of an acidic quality in the experiment after two months at sea, when the ship was already afflicted with scurvy. He divided twelve scorbutic sailors into six groups of two. They all received the same diet but, in addition, group one was given a quart of cider daily, group two twenty-five drops of elixir of vitriol (sulphuric acid), group three six spoonful of vinegar, group four half a pint of seawater, group five received two branches and one lemon, and the last group a spicy paste plus a drink of barley water. The treatment of group five stopped after six days when they ran out of fruit, but by then one sailor was fit for duty while the other had almost recovered. Apart from that, only group one also showed some effect of its treatment,[20,32]

After 1750, the discipline began to take its modern shape. John Haygarth demonstrated the importance of a control group for the correct identification of the placebo effect in his celebrated study of the ineffective remedy called Perkin's tractor.[19] Further work in that direction was carried out by the eminent physician Sir William Gull, 1st Baronet in the 1860s.[15] Frederick Akbar Mohamed (d. 1884), who worked at Guy's Hospital in London, made substantial contributions to the process of clinical trials, where "he separated chronic nephritis with secondary hypertension from what we now term essential hypertension.[33] He also founded the Collective Investigation Record for the British Medical Association that collected data from physicians practicing outside the hospital setting and was the precursor of modern collaborative clinical trials.[23,34]

The Genesis of Modern Clinical trials

Austin Bradford Hill was an important figure in the modern development of clinical trials. Sir Ronald A Fischer, while working for the Rothamsted experimental station in the field of agriculture, developed his *Principles of experimental design* in the 1920s as an accurate methodology for the proper design of experiments. Among his major ideas, was the importance of randomization, the random assignment of individuals to different groups for the experiment[24,35] replication to reduce uncertainty, the need for measurements to be repeated and experiments replicated to identify sources of variation.[25,36] He introduced blocking to arrange experimental units into groups of units that are similar to each other, and thus reducing irrelevant sources of variation; the use of factorial experiments efficient at evaluating the effects and possible interactions of several independent factors.[15,36]

The British Medical Research Council officially recognized the importance of clinical trials from the 1930s, when the council established the *Therapeutic Trials Committee* to advise and assist in the arrangement of properly controlled clinical trials on new products that seem likely on experimental grounds to have value in the treatment of disease.[5,37] The first randomized therapeutic trial was carried out at the medical research council (MRC) Tuberculosis Research Unit by Sir Geoffrey Marshall (1887–1982).[9] The trial, carried out between 1946 and 1947, was to test the efficacy of the chemical streptomycin for treating pulmonary tuberculosis. The trial was both a double-blind and placebo-control.[38] The methodology of clinical trials was further developed by Sir Austin Bradford Hill, who had been involved in the streptomycin trials. From the 1920s, Hill applied statistics to medicine, attending the lectures of renowned mathematician Karl Pearson, among others. He became famous for a landmark study carried out in collaboration with Richard Dill on the correlation between smoking and lung cancer.[14,39] They carried out a case-control study in 1950, which compared lung cancer patients with matched control and also began a sustained long-term prospective study into the broader

issue of smoking and health, which involved studying the smoking habits and health of more than 30000 doctors over a period of several years.[40] His certificate for admission into the Royal Society called him the leader in the development in medicine of the precise experimental methods now used nationally and internationally in the evaluation of new therapeutic and prophylactic agents.[41]

Types of clinical trials

Trials are classified by their purpose. After approval for human research is granted to the trial sponsor, the U.S. Food and Drug Administration (FDA) organizes and monitors the results of trials according to type.[29]

Open Label clinical trials: The doctor and patients know which drug or vaccine is being administered while in blinded clinical trial there is single blind where the patient does not know which treatment, he/she is getting, while for double blind, neither the doctor nor patient knows the treatment being administered.[11,42]

Placebo control

The new treatment is tested against an inactive (or dummy) treatment that looks the same Placebo control is only recommended for use when there are no standard referenced control drugs in the market. It is not highly recommended by the Helsinki Declaration of 1998.[12,43]

Pilot study: A small study that helps develop bigger study. A first attempt into a particular area used to explore the possibility of conducting a study with potential anticipated difficulties and can help with the design of the bigger, more pivotal study.[44]

Prevention trials

They are trails to evaluate the effectiveness of ways to reduce the risk of a disease or prevent the recurrence of a disease. This involves enrolling healthy people at high risk for developing a disease like in cancer predisposition. This trial assesses new means of detecting disease earlier in healthy subjects.[44]

Early detection/screening diagnosis

This trial test the best way to detect early a potential disease, like for example in cancer by use of Pap smears, Mammograms. Blood tests, X-rays, detect disease at an earlier stage, resulting in improved outcomes with use of biomarkers.[13,45]

Diagnostic trials

Focus is to develop better tools for classifying types and phases of a developing disease, etiology and managing patient care. Usually include people who have signs or symptoms of classic diseases.[19,46]

Quality of life/supportive studies

Aim at improving comfort and quality of life for patients and their families.

Genetic trials

For the determination of how one's genetic makeup can influence detection, diagnosis, prognosis, and treatment. Broaden understanding of causes of diseases like poverty related diseases (PRD) and emerging Diseases.[15] Develop targeted treatments based on the genetics of a disease. In an observational study, the investigators observe the subjects and measure their outcomes. The researchers do not actively manage the study.[30,46] In an *interventional study*, the investigators give the research subjects an experimental drug, surgical procedure, use of a medical device, diagnostic or other intervention to compare the treated subjects with those receiving no treatment or the standard treatment. Then the researchers assess how the subjects' health changes.[30]

Epidemiological Trials

Epidemiological trials have the goal of identifying the general causes, patterns or control of diseases in large numbers of people.[46]

***Compassionate use* trials**

Compassionate use or expanded access trials provide partially tested, unapproved therapeutics to a small number of patients who have no other realistic options. Usually, this involves a disease for which no effective therapy has been approved, or a patient who has already failed all standard treatments and whose health is too compromised to qualify for participation in randomized clinical trials.[31,47] Usually, case-by-case approval must be granted by both the FDA and the pharmaceutical company for such exceptions.

Fixed trials

Fixed trials consider existing data only during the trial's design, do not modify the trial after it begins, and do not assess the results until the study is completed.

Adaptive clinical trials

This trial use existing data to design the trial, and then use interim results to modify the trial as it proceeds. Modifications include dosage, sample size, drug undergoing trial, patient selection criteria and "cocktail" mix.[32] Adaptive trials often employ a Bayesian experimental design to assess the trial's progress. In some cases, the trials have become an ongoing process that regularly adds and drops therapies and patient groups as more information is gained.[48] The aim is to quickly identify drugs that have a therapeutic effect and to focus on patient populations for whom the drug is appropriate.[34,35,49]

Pre-Clinical investigation

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 (mechanisms of action, and the relationship between drug levels and clinical response),

and 3) pharmacokinetics (drug absorption, distribution, metabolism, excretion, and potential drug–drug interactions). This data must be submitted for Investigational New Drug (IND) approval if the drug is to be further studied in human subjects.[15] The FDA emphasis is on "safety first," and therefore it is logical that the phases of clinical trials are designed to test the safety and maximum tolerated dose (MTD) of a drug, human pharmacokinetics and pharmacodynamics, and drug–drug interactions.[30,31]

Clinical Trials Phases

Clinical trials are conducted typically in four phases, with each phase using different numbers of subjects and having a different purpose to construct focus on identifying a specific effect.[29,50] Clinical trials involving new drugs are commonly classified into five phases. Each phase of the drug approval process is treated as a separate clinical trial.[35] The drug development process will normally proceed through phases I–IV over many years, frequently involving between 10-15 years.[21] If the drug successfully passes through phases I, II, and III, it will usually be approved by the national regulatory authority for use in the general population.[51] Phase IV trials are then performed after the newly approved drug, diagnostic or device is marketed, providing assessment about risks, benefits, or best uses.[52]

Phase 0

Phase 0 is a recent designation for optional exploratory trials conducted in accordance with the United States Food and Drug Administration (FDA) 2006. Guidance on Exploratory Investigational New Drug (IND) Studies. Phase 0 trials are also known as human micro-dosing studies and are designed to speed up the development of promising drugs or imaging agent by establishing very early on whether the drug or agent behaves in human subjects as was expected from preclinical studies.[9,17,53] Distinctive features of Phase 0 trials include the administration of single subtherapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics. A Phase 0 study gives no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect.

Phase 1

The phase I trials (synonymous with "dose-escalation" or "human pharmacology" studies) are the first time in which the new investigational compound is studied in humans, and are usually performed open label and in a small number of "healthy" and/or "diseased" volunteers.[54] The MTD, or the drug dose is selected before a dose-limiting toxicity, can be determined using various statistical designs. Dose escalation is based on very strict criteria, and subjects are closely followed for evidence of drug toxicity over a defined time period.[23,55] There is a risk that subjects who volunteer or the actual physicians who enroll patients for phase I studies could misinterpret its objective as therapeutic. For example, despite strong evidence that objective response rates in phase I trials of chemotherapeutic drugs is exceedingly low (as low as 2.5%)[22], patients may still have a "therapeutic misconception" of potentially receiving a direct medical benefit from trial participation.[23] The improvement of the informed consent process could help address some of these misconceptions while still maintaining adequate enrollment numbers.[56]

Phase II

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.[27,57] They are designed to test safety, pharmacokinetics, and pharmacodynamics, but may also be designed to answer questions important for the planning of phase III trials, including determination of optimal doses, dose frequencies, administration routes, and endpoints. Furthermore, they may offer preliminary evidence of drug efficacy by: 1) comparing the drug in study 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).[58] Here, the small number of participants and primary safety concerns within a phase II trial usually limit its power to establish efficacy, and therefore supports the necessity of a subsequent phase III trial.[31,59] 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).[60] The Manufacturing concerns may also be discussed at this stage depending on the concerns with the drug product.

Phase III

Phase III Trials is initiated based on prior studies demonstrating drug safety and potential efficacy. This phase III trial (also referred to as a "therapeutic confirmatory," "comparative efficacy," or "pivotal trial") may be pursued.[25,61] 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.[63] 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 (based on Hanley's "Rule of 3").[32] This highlights the significance of phase IV trials in identifying less-common adverse drug reactions, and this is the one reason why the FDA usually requires more than one phase III trial to establish drug safety and efficacy.[64] 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 or a placebo.[11,65] Even in 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.[66] This further highlights the uniqueness of study participants and why a trial may lack external validity. The application of placebos, including surgical placebos ("sham procedures"), has triggered great debate; the revised Declaration of Helsinki supports comparative efficacy trials by discouraging the use of drug placebos in favour of "best current" treatment controls.[3,41,67] Another type of phase III trial, the equivalency trial (or "positive-control study"), is designed to ascertain whether the experimental treatment is similar to the chosen comparator within some margin prespecified by the investigator.[68] Therefore, a placebo is almost never included in current study design. As long as the differences between the intervention and the comparator remain within the prespecified margin, the intervention will be deemed equivalent to the comparator.[53,69,70]

Although the prespecified margin is often based on external evidence, statistical foundations, and clinical experience, there still remains a little guidance for setting acceptable margins. A variant of the equivalency trial, the noninferiority study, is conducted with the goal of excluding the possibility that the experimental intervention is less effective than the standard treatment by some prespecified magnitude.[4,71] Caution is required when interpreting the results of all types of equivalency trials because they are often incorrectly designed and analyzed as if they were comparative efficacy studies.[23,39] Such flaws can result in a bias towards the null, which would translate into a false-negative result in a comparative efficacy study, but a false-positive result in an equivalency trial. It is important to note that the noninferiority trial is more susceptible to false-positive results than other study designs.[31] The highlight of the phase III trial design is the balance in treatment allocation for comparison of treatment efficacy. This is implemented through randomization, as a modern clinical trial practice which attempts to eliminate imbalance of confounders and/or any systematic differences (or biases) between treatment groups.[72]

The statistical tool of randomization, clinical trials by Sir Austin Bradford Hill, was born out of the necessity (and ethical justification) of rationing limited supplies of streptomycin in a British trial of pulmonary tuberculosis.[5] The most basic randomization model, simple randomization, randomly allocates each subject to a trial arm regardless of those already assigned (ie, a "coin flip" for each subject). Although easy to perform, major imbalances in treatment assignments or distribution of covariates can ensue, making this strategy less than ideal.[11,73] To improve on this method, a constraint can be placed on randomization that forces the number of subjects randomly assigned per arm to be equal and balanced after a specified block size ("block randomization"). For instance, considering 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. The limitation 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.".[74] 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 (eg, a block size of 4 followed by a block size of 8 followed by a block size of 6).[75]

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). Stratification facilitates analysis by ensuring that specific prognostic factors of presumed clinical importance are properly balanced in the arms of a clinical trial.[16,44,76] Stratification of a relatively small sample size that has also undergone block randomization may result in loss of the originally intended balance, thereby supporting the merits of alternative techniques such as minimization or dynamic allocation, designed to reduce imbalances among multiple strata and study arms.[34] In most cases, 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 reduce this "information bias" include "single blinding" (subject only), "double blinding" (both subject and investigator), or "triple blinding" (data analyst, subject, and investigator).[49,77] Unfortunately, not all trials can be blinded for example, 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. When appropriate, additional strategies can be applied to enhance study efficiency, such as assigning each subject to serve as his/her own control (crossover study) or evaluating more than one treatment simultaneously (factorial design).[78]

The most common approach to analyzing phase III trials is the intention-to-treat analysis, in which subjects are assessed based on the intervention arm to which they were randomized, irrespective of what treatment they actually received. This is commonly known as the "analyzed as randomized" rule. A complementary or

secondary analysis is an "as-treated" or "per-protocol" analysis, in which subjects are evaluated based on the treatment they actually received, regardless of whether they were randomized to that treatment arm. Intention-to treat analyses are preferable for the primary analysis of RCTs.[23,79] As they eliminate selection bias by preserving randomization; any difference in outcomes can therefore be attributed to the treatment alone and not confounders. In contrast, an "as-treated" or "per-protocol" approach may eliminate any benefit of random treatment selection in an interventional trial, as it estimates the effect of treatment received.[80] The study thereby becomes similar to an interventional cohort study with the potential for treatment selection bias. If adherence in the treatment arm is poor and contamination in the control group is high, an intention-to-treat analysis may fail to show a difference in outcomes.[38] This is in contrast to a per-protocol analysis that takes into account these protocol violations. Based on the vast combination of strategies applicable to the design of a phase III study, the Consolidated Standards of Reporting Trials (CONSORT) guideline was established to improve the quality of trial reporting and assist with evaluating the conduct and validity of trials and their results.[81]

Phase IV

Phase IV Trials is initiated once a drug has been approved by a regulatory authority. The FDA in particular, may require that a sponsor conduct a phase IV trial as a stipulation for drug approval, although less than half of such studies are actually completed or even initiated by sponsors [38, 82]. Phase IV trials, also referred to as "therapeutic use" or "post-marketing" studies, are observational studies performed on FDA-approved drugs to meet the following objectives: 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.[83] 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.[39,40] As described by pharmaco-epidemiologists, "this reflects a deliberate societal decision to balance delays in access to new drugs with delays in information about rare adverse reactions.[41] Over the past two decades, there has been a steady rise in voluntarily and spontaneously reported serious adverse drug reactions submitted to the FDA's.[42] Reports are submitted directly by physicians and consumers, or indirectly via drug manufacturers (the most common route).[84] Weaknesses of this post-marketing surveillance can be illustrated using the case of failures to quickly detect serious cardiovascular events resulting from the use of the anti-inflammatory medication Vioxx® and prescription diet drug Meridia®.[14,58,85] It was only after the European SCOUT (Sibutramine Cardiovascular OUTcome Trial) study, driven by anecdotal case reports concerning cardiovascular safety, that the FDA withdrew Meridia® from the market in the late 2010.[43]

The most common criticisms of the FDA's post-marketing surveillance can be outline as follows: 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.[9,38,41] Proposed solutions include the establishment of a national health data network to oversee post-marketing surveillance independent of the FDA-approval process[44], preplanned meta-analyses of a series of related trials to assess less-common adverse events[45] and large-scale simple RCTs with few eligibility and treatment criteria.[46]

A summarized table of clinical trials scope, objectives and outcome is illustrated in table 1 and in figure 2.

Table of Clinical trials, scope and objectives with outcomes.

Trials Phase	Scope and Objective	Trials Outcomes	Reference
Phase 0	Pharmacokinetics particularly oral bioavailability and half-life of the drug & Pharmacodynamics in humans	Phase 0 trials are optional first-in-human trials. Single subtherapeutic doses of the study drug or treatment are given to a small number of subjects (typically 10 to 15) to gather preliminary data on the agent's pharmacodynamics (what the drug does to the body) and pharmacokinetics (what the body does to the drugs). For a test drug, the trial documents the absorption, distribution, metabolization, and clearance (excretion) of the drug, and the drug's interactions within the body, to confirm that these appear to be as expected.	[38]
Phase I	Screening for safety	Often are first-in-person trials. Testing within a small group of people (typically 20–80) to evaluate safety, determine safe dosage ranges, and identify side effects.	[27,29]
Phase II	Proof of preliminary efficacy of the drug in a treatment group with a	Phase IIa is specifically designed to assess dosing requirements (how much drug should be given), while a	[29,3]

	comparator (proof of superiority), usually against a placebo control group	Phase IIb trial is designed to determine efficacy, and studies how well the drug works at the prescribed dose(s), establishing a therapeutic dose range.	
Phase III	Final confirmation of safety and efficacy	Testing with large groups of people (typically 1,000–3,000) to confirm its efficacy, evaluate its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely.	[29]
Phase IV	Safety studies during sales	Postmarketing studies delineate risks, benefits, and optimal use. As such, they are ongoing during the drug's lifetime of active medical use.	[29]

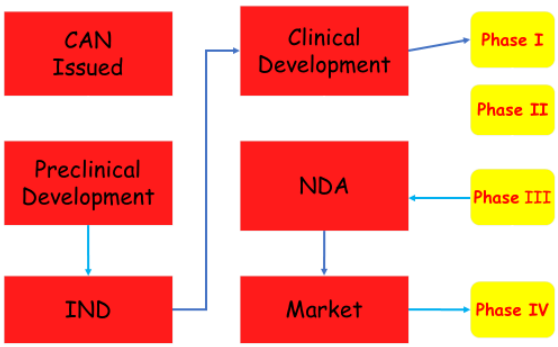

Figure 2: New chemical entity development process from drug candidate (CAN) to marketed product.[25]

Clinical Trial design

A fundamental distinction in evidence-based practice is between observational studies and randomized control trials.[38] Types of observational studies in epidemiology, such as the cohort study and the case control study, provide less compelling evidence than the randomized controlled trial.[86] In observational studies, the investigators retrospectively assess associations between the treatments given to participants and their health status, with potential for considerable errors in design and interpretation.[39] A randomized controlled trial can provide compelling evidence that the study treatment causes an effect on human health.[39] Currently, some Phase II and most Phase III drug trials are designed as randomized double-blind and placebo-controlled.

Randomized: Each study subject is randomly assigned to receive either the study treatment or a placebo.

Blind: The subjects involved in the study do not know which study treatment they receive. If the study is double-blind, the researchers also do not know which treatment a subject receives.[87] This intent is to prevent researchers from treating the two groups differently. A form of double-blind study called a "double-dummy" design which allows additional insurance against bias. In this kind of study, all patients are given both placebo and active doses in alternating periods.[12,88]

Placebo-controlled: The use of a placebo (fake treatment) allows the researchers to isolate the effect of the study treatment from the placebo effect.[6] Clinical studies having small numbers of subjects may be "sponsored" by single researchers or a small group of researchers, and are designed to test simple questions or feasibility to expand the research for a more comprehensive randomized controlled trial.[5,40]

Active control studies

In most cases, giving a placebo to a person suffering from a disease may be unethical[17] and therefore, to address this, it has become a common practice to conduct "active comparator" (also known as "active control") trials. In this study an active control group, subjects are given either the experimental treatment or a previously approved treatment with known effectiveness.[89]

Master protocol

In this study, multiple experimental treatments are tested in a single trial. Genetic testing enables researchers to group patients according to their genetic profile, deliver drugs based on that profile to that group and compare the results. Multiple companies can participate, each bringing a different drug.[2,90] The first of such study was to approach targets squamous cell cancer, which includes varying genetic disruptions from patient to patient. Amgen, AstraZeneca and Pfizer were involved, the first time they worked together in a late-stage trial. Patients whose genomic profiles do not match any of the trial drugs received a drug designed to stimulate the immune system to attack cancer.[42]

Clinical trial protocol

A clinical trial protocol is a document used to define and manage the trial. It is prepared by a panel of experts and all the study investigators are expected to strictly observe the protocol.[15] The protocol describes the scientific rationale, objective(s), design, methodology, statistical considerations and organization of the planned trial. Details of the trial are provided in documents referenced in the protocol, such as an investigator's brochure.[91] The protocol contains a precise study plan to guarantee safety and health of the trial subjects, and to provide an exact template for trial conduct by investigators. This allows data to be combined across all investigators/sites. The protocol also informs the study administrators who in some cases may be a contract research organization. The format and content of clinical trial protocols sponsored by pharmaceutical, biotechnology or medical device companies in the United States, European Union, or Japan have been standardized to follow Good Clinical Practice guidance.[9,43,92], issued by the International

Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[44]

Clinical Trials Design features

Clinical trials recruit study subjects to sign a document representing their informed consent.[93] The document includes details such as its purpose, duration, required procedures, risks, potential benefits, key contacts and institutional requirements.[2, 46] The participant then decides whether to sign the document. The document is not a contract, as the participant can withdraw at any time without penalty.[55] Informed consent is a legal process in which a recruit is instructed about key facts before deciding whether to participate. Researchers explain the details of the study in a manner and language the subject can understand. The information is presented in the subject's native language. Generally, children cannot autonomously provide informed consent, but depending on their age and other factors, may be required to provide informed assent.

Clinical trials Statistical power

In any clinical trial, the number of subjects, also called the sample size, has a large impact on the ability to reliably detect and measure the effects of the intervention. This ability is described as its power, which must be calculated before initiating a study to determine if the study is worth its costs.[47] In general, a larger sample size increases the statistical power, and also the cost of the study. The statistical power estimates the ability of a trial to detect a difference of a particular size (or larger) between the treatment and control groups. For instance, a trial of a lipid-lowering drug versus placebo with 100 patients in each group might have a power of 0.90 to detect a difference between placebo and trial groups receiving dosage of 10 mg/dL or more, but only 0.70 to detect a difference of 6 mg/dL.[93]

Placebo groups

In all cases of clinical trials just giving a treatment can have nonspecific effects and therefore these are controlled for by the inclusion of patients who receive only a placebo.[21,66] Subjects are assigned randomly without informing them to which group they belonged. Many trials are double-blinded so that researchers do not know to which group a subject is assigned. Assigning a subject to a placebo group can pose an ethical problem if it violates his or her right to receive the best available treatment. The Declaration of Helsinki provides guidelines on this issue.[40]

Clinical Research Time lines/Duration

The drug development process is a long process with huge financial implication and risk taking. The process can take 10-15 years from discovery of hit to market product. This time lines have been illustrated in figure 4.

Figure 4: Clinical research drug development time lines.[17]

Clinical trials are only a small part of the research that goes into developing a new treatment. Potential drugs, for example, first have to be discovered, purified, characterized, and tested in labs (in cell and animal studies) before ever undergoing clinical trials. In all, about 1,000 potential drugs are tested before just one reaches the point of being tested in a clinical trial.[3,18] For example, a new cancer drug has, on average, six years of research behind it before it even makes it to clinical trials. But the major obstacle in making new cancer drugs available is the time it takes to complete clinical trials themselves. On average, about eight years pass from the time a cancer drug enters clinical trials until it receives approval from regulatory authorities for sale to the public.[53]

Some reasons a clinical trial might last several years

For chronic conditions such as cancer, it takes months, if not years, to see if a cancer treatment has an effect on a patient. For drugs that are not expected to have a strong effect (meaning a large number of patients must be recruited to observe 'any' effect), recruiting enough patients to test the drug's effectiveness (i.e., getting statistical power) can take several years. Only certain people who have the target disease condition are eligible to take part in each clinical trial. Researchers who treat

these particular patients must participate in the trial. Then they must identify the desirable patients and obtain consent from them or their families to take part in the trial. A clinical trial might also include an extended post-study follow-up period from months to years for people who have participated in the trial, a so-called "extension phase", which aims to identify long-term impact of the treatment.[17,51] The biggest barrier to completing studies is the shortage of people who take part. All drug and many device trials target a subset of the population, meaning not everyone can participate. Some drug trials require patients to have unusual combinations of disease characteristics. It is a challenge to find the appropriate patients and obtain their consent, especially when they may receive no direct benefit (because they are not paid, the study drug is not yet proven to work, or the patient may receive a placebo). In the case of cancer patients, fewer than 5% of adults with cancer will participate in drug trials.

According to the Pharmaceutical Research and Manufacturers of America (PhRMA), about 400 cancer medicines were tested in clinical trials in 2005. Not all of these were proven to be useful, but those that were delayed in getting approved because the number of participants were so low 51]. For clinical trials involving potential for seasonal influences (such as airborne allergies, seasonal affective disorder, influenza, and skin diseases), the study may be done during a limited part of the year (such as spring for pollen allergies), when the drug can be tested.[11,22] Clinical trials that do not involve a new drug usually have a much shorter duration. (Exceptions are epidemiological studies, such as the Nurses Health Study.

Clinical Trial Administration

Clinical trials are headed by a Principal Investigator. In some countries like in the US clinical trials designed by a local investigator can be federally funded and administered by the researcher who designed the study and applied for the grant. Small-scale device studies may be administered by the sponsoring company. Clinical trials of new drugs are usually administered by a contract research organization (CRO) hired by the sponsoring company. The sponsor provides the drug and medical oversight. A CRO is contracted to perform all the administrative work on a clinical trial. For Phases II–IV the CRO recruits participating researchers, trains them, provides them with supplies, coordinates study administration and data collection, sets up meetings, monitors the sites for compliance with the clinical protocol, and ensures the sponsor receives data from every site. Specialized site management organizations can also be hired to coordinate with the CRO to ensure rapid IRB/IEC approval and faster site initiation and patient recruitment. Phase I clinical trials of new medicines are often conducted in a specialist clinical trial clinic, with dedicated pharmacologists, where the subjects can be observed by full-time staff. These clinics are often run by a CRO which specializes in these studies.[6,92]

At a participating site, one or more research assistants (often nurses) do most of the work in conducting the clinical trial. The research assistant's job can include some or all of the following: providing the local Institutional review board (IRB) with the documentation necessary to obtain its permission to conduct the study, assisting with study start-up, identifying eligible patients, obtaining consent from them or their families, administering study treatment(s), collecting and statistically analyzing data, maintaining and updating data files during follow up, and communicating with the IRB, as well as the sponsor and CRO.[21]

Clinical Research Quality

Within the context of a clinical trial, quality generally refers to the absence of errors which can impact decision making, both during the conduct of the trial and in use of the trial results.[3,46]

Marketing

Making of clinical trial is very important for effective participation of the community. Janet Yang for example uses the Interactional Justice Model to test the effects of willingness to talk with a doctor and clinical trial enrollment [5, 19]. Results found that potential clinical trial candidates were less likely to enroll in clinical trials if the patient was more willing to talk with their doctor. The reasoning behind this discovery may be that patients are happy with their current care. Another reason for the negative relationship between perceived fairness and clinical trial enrollment is the lack of independence from the care provider. Results have shown that there is a positive relationship between a lack of willingness to talk with their doctor and clinical trial enrollment. Lack of willingness to talk about clinical trials with current care providers may be due to patients' independence from the doctor. Patients who are less likely to talk about clinical trials are more willing to use other sources of information to gain a better insight of alternative treatments. Clinical trial enrollment should be motivated to utilize websites, television, community assembly groups like churches, use of community engagement groups to advertise and inform the public about clinical trial enrollment.[67]

Information technology

The last decade has seen a proliferation of information technology use in the planning and conduct of clinical trials. Clinical trial management systems are often used by research sponsors or CROs to help plan and manage the operational aspects of a clinical trial, particularly with respect to investigational sites. Advanced analysis for identifying researchers and research sites with expertise in a given area utilize public and private information about ongoing research.[33] Web-based electronic data capture (EDC) and clinical data management systems (CDMS), are used in a majority of

clinical trials[40,41], to collect case report data from sites, manage its quality and prepare it for analysis. Interactive voice response systems are used by sites to register the enrollment of patients using a phone and to allocate patients to a particular treatment arm (although phones are being increasingly replaced with web-based (IWRS) tools which are sometimes part of the EDC system). While patient-reported outcome were often paper based in the past, measurements are increasingly being collected using web portals or hand-held ePRO (or e Diary) devices, sometimes wireless.[41] Statistical software is used to analyze the collected data and prepare them for regulatory submission. Access to many of these applications are increasingly aggregated in web-based clinical trials portals. In 2011, the FDA approved a Phase I trial that used telemonitoring, also known as remote patient monitoring, to collect biometric data in patients' homes and transmit it electronically to the trial database. This technology provides many more data points and is far more convenient for patients, because they have fewer visits to trial sites.

Ethical consideration in clinical trials

Clinical trials are closely supervised by appropriate regulatory authorities. All studies involving a medical or therapeutic intervention on patients must be approved by a supervising ethics committee before permission is granted to run the trial.[77] The local ethics committee has discretion on how it will supervise noninterventional studies (observational studies or those using already collected data). This body is called the Institutional Review board (IRB); or Ethics Committees (Ecs). Most IRBs are located at the local investigator's hospital or institution, but some sponsors allow the use of a central (independent/for profit) IRB for investigators who work at smaller institutions. To be ethical, researchers must obtain the full and informed consent of participating human subjects. (One of the IRB's main functions is to ensure potential patients are adequately informed about the clinical trial.) If the patient is unable to consent for him/herself, researchers can seek consent from the patient's legally authorized representative.[69] In most countries, the local IRB must certify researchers and their staff before they can conduct clinical trials. In cases like in the US researchers must understand the federal patient privacy (HIPAA) law and good clinical practice. The International Council of Harmonization Guidelines for Good Clinical Practice is a set of standards used internationally for the conduct of clinical trials. The guidelines aim to ensure the "rights, safety and wellbeing of trial subjects are protected".[16,38] The notion of informed consent of participating human subjects exists in many countries but its precise definition may still vary.

Informed consent is clearly a 'necessary' condition for ethical conduct but does not 'ensure' ethical conduct. In compassionate use trials the latter becomes a particularly difficult problem.[3] The final objective is to serve the community of patients or future patients in a best-possible and most responsible manner. However, it may be hard to turn this objective into a well-defined, quantified, objective function. In some cases, this can be done, however, for instance, for questions of when to stop sequential treatments and then quantified methods may play an important role. Additional ethical concerns are present when conducting clinical trials on children (pediatrics), and in emergency or epidemic situations.[35,44] Ethically balancing the rights of multiple stakeholders may be difficult. For example, when drug trials fail, the sponsors may have a duty to tell current and potential investors immediately, which means both the research staff and the enrolled participants may first hear about the end of a trial through public business news.[35]

Conflicts of interest and unfavorable studies

The specific problem in which unfavorable data from pharmaceutical company-sponsored research were not published, in order to address this problem, the Pharmaceutical Research and Manufacturers of America published new guidelines urging companies to report all findings and limit the financial involvement in drug companies by researchers.[13,36] The US Congress for example also signed into law a bill which requires Phase II and Phase III clinical trials to be registered by the sponsor on the clinicaltrials.gov website compiled by the National Institutes of Health.[93] Drug researchers not directly employed by pharmaceutical companies often seek grants from manufacturers, and manufacturers often look to academic researchers to conduct studies within networks of universities and their hospitals. Similarly, competition for tenured academic positions, government grants and prestige create conflicts of interest among academic scientists.[27] According to one study, approximately 75% of articles retracted for misconduct-related reasons have not declared industry financial support[76] Seeding trials are particularly controversial.[37]

All clinical trials submitted in the US to the FDA as part of a drug approval process are independently assessed by clinical experts within the Food and Drug Administration[7,29], including inspections of primary data collection at selected clinical trial sites.[44] In 2001, the editors of 12 major journals issued a joint editorial, published in each journal, on the control over clinical trials exerted by sponsors, particularly targeting the use of contracts which allow sponsors to review the studies prior to publication and withhold publication. They strengthened editorial restrictions to counter the effect. The editorial noted that contract research organizations had, by 2000, received 60% of the grants from pharmaceutical companies in the US. Researchers may be restricted from contributing to the trial design, accessing the raw data, and interpreting the results.[31]

Despite explicit recommendations by stakeholders of measures to improve the standards of industry-sponsored medical research[85], in 2013, Tohen warned of the

persistence of a gap in the credibility of conclusions arising from industry-funded clinical trials, and called for ensuring strict adherence to ethical standards in industrial collaborations with academia, in order to avoid further erosion of the public's trust.[55,62]

Clinical trials during public health crises

The conduct of clinical trials of vaccines or new chemical entities during epidemics and pandemics is subject to ethical concerns. For diseases with high mortality rates like Ebola, assigning individuals to a placebo or control group can be viewed as a death sentence.[89] In response to ethical concerns regarding clinical research during epidemics, the National Academy of Medicine authored a report identifying seven ethical and scientific considerations.[33] These considerations are; Scientific value, Social value, Respect for persons, Community engagement, Concern for participant welfare and interests, A balance towards benefit over risks, Post-trial access to tested therapies that had been withheld during the trial.[13,47,66]

Clinical trials on Pregnant women and children

Pregnant women and children are usually excluded from clinical trials being considered as vulnerable populations, though the data to support excluding them is not robust. By excluding them from clinical trials, information about the safety and effectiveness of therapies for these populations is often lacking.[2,9] During the early history of the HIV/AIDS epidemic, a scientist noted that by excluding these groups from potentially life-saving treatment, they were being "protected to death". Projects such as Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) have advocated for the ethical inclusion of pregnant women in vaccine trials.[65,72] Inclusion of children in clinical trials has additional moral considerations, as children lack decision-making autonomy. Trials in the past had been criticized for using hospitalized children or orphans; these ethical concerns effectively stopped future research. In efforts to maintain effective pediatric care, several European countries and the US have policies to entice or compel pharmaceutical companies to conduct pediatric trials. International guidance recommends ethical pediatric trials by limiting harm, considering varied risks, and taking into account the complexities of pediatric care.[83]

Clinical trials Safety

The responsibility for the safety of subjects in a clinical trial is shared between the sponsor, the local site investigators (if different from the sponsor), the various IRBs that supervise the study, and (in some cases, if the study involves a marketable drug or device), the regulatory agency for the country where the drug or device will be sold.[75,88] A systematic concurrent safety review is frequently employed to assure research participant safety. The conduct and on-going review is designed to be proportional to the risk of the trial. In most cases, this role is filled by a Data and Safety Committee, an externally appointed Medical Safety Monitor[17] an Independent Safety Officer, or for small or low-risk studies the principal investigator[17] For safety reasons, many clinical trials of drugs are designed to exclude women of childbearing age, pregnant women, or women who become pregnant during the study. In some cases, the male partners of these women are also excluded or required to take birth control measures.[33,55,90]

Sponsor of clinical trials

In the whole clinical trial process, the sponsor is responsible for accurately informing the local site investigators of the true historical safety record of the drug, device or other medical treatments to be tested, and of any potential interactions of the study treatment(s) with already approved treatments.[29] This allows the local investigators to make an informed decision on whether to participate in the study or not. The sponsor is also responsible for monitoring the results of the study as they come in from the various sites as the trial proceeds.[31,44] In larger clinical trials, a sponsor will use the services of a data monitoring committee (DMC, known as a data safety monitoring board). This independent group of clinicians and statisticians meets periodically to review the unblinded data the sponsor has received so far. The DMC has the power to recommend termination of the study based on their review, for example if the study treatment is causing more deaths than the standard treatment, or seems to be causing unexpected and study-related serious adverse events. The sponsor is responsible for collecting adverse event reports from all the sites for investigators in the study, and for informing all the investigators of the sponsor's judgment as to whether these adverse events were related or not related to the study treatment.

The sponsor and the local site investigators are jointly responsible for writing a site-specific informed consent that accurately informs the potential subjects of the true risks and potential benefits of participating in the study, while at the same time presenting the material as briefly as possible and in ordinary language. The FDA regulations states that participating in clinical trials is voluntary, with the subject having the right not to participate or to end participation at any time.[5,44]

Local site investigators

The ethical principle of *primum non-nocere* ("first, do no harm") guides the trial, and if an investigator believes that the study treatment may be harmful to subjects in the study, the investigator can stop participation at any time. On the other hand, investigators often have a financial interest in recruiting subjects, and could act unethically to obtain and maintain their participation.[77]

The local investigators are responsible for conducting the study according to the study protocol, and supervising the study staff throughout the duration of the study. The local investigator or his/her study staff are also

responsible for ensuring that the potential subjects in the study understand the risks and potential benefits of participating in the study. In other words, they (or their legally authorized representatives) must give their informed consent (preferably written), Local investigators are responsible for reviewing all adverse event reports sent by the sponsor. These adverse event reports contain the opinions of both the investigator (at the site where the adverse event occurred) and the sponsor, with respect to the relationship of the adverse event to the study treatments. Local investigators also are responsible for making an independent judgment of these reports, and promptly informing the local IRB of all serious and study treatment-related adverse events.[78,91] When a local investigator is the sponsor, there may not be formal adverse event reports, but study staff at all locations are responsible for informing the coordinating investigator of anything unexpected. The local investigator is responsible for being truthful to the local IRB in all communications relating to the study.

Institutional review boards (IRBs)

Approval by an Institutional Review Board (IRB)), or Independent Ethics Committee (IEC), is necessary before any clinical study begin. In commercial clinical trials, the study protocol is not approved by an IRB before the sponsor recruits' sites to conduct the trial. However, the study protocol and procedures have been tailored to fit generic IRB submission requirements. In this case, and where there is no independent sponsor, each local site investigator submits the study protocol, the consent(s), the data collection forms, and supporting documentation to the local IRB. Universities and most hospitals have in-house IRBs. Other researchers (such as in walk-in clinics) use independent IRBs.

The IRB reviews the study both for medical safety and for protection of the patients involved in the study, before it approves and gives ethical clearance for the researcher to begin the study. It may require changes in study procedures or in the explanations given to the patient. A required yearly "continuing review" report from the investigator updates the IRB on the progress of the study and any new safety information related to the study.[31]

Regulatory agencies

In most developed countries like in the US, the FDA can audit the files of local site investigators after they have finished participating in a study, to see if they were correctly following study procedures. This audit may be random, or for cause (because the investigator is suspected of fraudulent data).[13] Avoiding an audit is an incentive for investigators to follow study procedures. A 'covered clinical study' refers to a trial submitted to the FDA as part of a marketing application (for example, as part of an NDA, about which the FDA may require disclosure of financial interest of the clinical investigator in the outcome of the study. For example, the applicant must disclose whether an investigator owns equity in the sponsor, or owns proprietary interest in the product under investigation. The FDA defines a covered study as "... any study of a drug, biological product or device in humans submitted in a marketing application or reclassification petition that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety.[31,86] Alternatively, many American pharmaceutical companies have moved some clinical trials overseas. Benefits of conducting trials abroad include lower costs (in some countries) and the ability to run larger trials in shorter timeframes, whereas a potential disadvantage exists in lower-quality trial management.[45,46] Different countries have different regulatory requirements and enforcement abilities. Globally an estimated 40% of all clinical trials now take place in Asia, Eastern Europe, and Central and South America. "There is no compulsory registration system for clinical trials in these countries and many do not follow European directives in their operations".[5,29] as reported by Jacob Sijtsma of the Netherlands-based WEMOS, an advocacy health organization tracking clinical trials in developing countries.[45]

From the 1980s, harmonization of clinical trial protocols was shown as feasible across countries of the European Union. At the same time, coordination between Europe, Japan and the United States led to a joint regulatory-industry initiative on international harmonization named after 1990 as the International Conference on Harmonization of Technical Requirements for registration of pharmaceuticals for human use (ICH).[72] Currently, most clinical trial programs follow ICH guidelines, aimed at "ensuring that good quality, safe and effective medicines are developed and registered in the most efficient and cost-effective manner. These activities are pursued in the interest of the consumer and public health, to prevent unnecessary duplication of clinical trials in humans and to minimize the use of animal testing without compromising the regulatory obligations of safety and effectiveness.[19]

Aggregation of safety data during clinical development

Aggregating safety data across clinical trials during drug development is important because trials are generally designed to focus on determining how well the drug works. The safety data collected and aggregated across multiple trials as the drug is developed allows the sponsor, investigators and regulatory agencies to monitor the aggregate safety profile of experimental medicines as they are developed.[78] The value of assessing aggregate safety data is: a) decisions based on aggregate safety assessment during development of the medicine can be made throughout the medicine's development and b) it sets up the sponsor and regulators well for assessing the medicine's safety after the drug is approved.[3,33,50]

Pharmacoeconomics

Clinical trial costs vary depending on the trial phase, type of trial, and the therapeutic disease area under study. A study of clinical trials conducted in the United States from 2014 to 2017 found the average cost of Phase I trials to be between $1.4 million and $6.6 million, depending on the type of disease. Phase II trials ranged from $7 million to $20 million, and Phase III trials from $11 million to $53 million.[94]

Participant recruitment and participation

Participants are recruited for a clinical study and therefore the recruitment strategy is important for a successful study participation. Different IRB define different recruitment strategy to help investigators avoid unethical channels for recruitment of participants. Newspaper advertisements are used to connect to patients and healthy volunteers seeking to participate in clinical trials. Phase 0 and Phase I drug trials seek healthy volunteers. Most other clinical trials seek patients who have a specific disease or medical condition. The diversity observed in society should be reflected in clinical trials through the appropriate inclusion of ethnic minority populations.[62] Patient recruitment or participant recruitment plays a significant role in the activities and responsibilities of sites conducting clinical trials.[53] All volunteers being considered for a trial are required to undertake a medical screening. Requirements differ according to the trial needs, but typically volunteers would be screened in a medical laboratory for the following; Measurement of the electrical activity of the heart (ECG), Measurement of blood pressure, heart rate, and body temperature, Blood sampling, Urine sampling, Weight and height measurement, Drug abuse testing and Pregnancy testing.[3.17,44,75] It has been reported that in developed countries like US participants in clinical trials are disproportionately white and vice versa for countries in sub-Sahara Africa. This may reduce the validity of findings in respect of non-white patients.[93]

Locating trials

Depending on the kind of participants required, sponsors of clinical trials, or contract research organizations working on their behalf, try to find sites with qualified personnel as well as access to patients who could participate in the trial. Working with those sites, they may use various recruitment strategies, including patient databases, newspaper and radio advertisements, flyers, posters in places the patients might go (such as doctor's offices), and personal recruitment of patients by investigators. In well developed and organized local communities in Africa, churches and community engagement groups play an important role in participant recruitments.

Volunteers with specific conditions or diseases have additional online resources to help them locate clinical trials. For example, the Fox Trial Finder connects Parkinson's disease trials around the world to volunteers who have a specific set of criteria such as location, age, and symptoms.[64] Other disease-specific services exist for volunteers to find trials related to their condition. Volunteers may search directly on Clinical Tials.gov to locate trials using a clinical trial registry run by the U.S National Institutes of Health and National Library of Medicine.

Clinical Research

The risk information seeking and processing (RISP) model analyzes social implications that affect attitudes and decision-making pertaining to clinical trials.[17] People who hold a higher stake or interest in the treatment provided in a clinical trial showed a greater likelihood of seeking information about clinical trials. Cancer patients reported more optimistic attitudes towards clinical trials than the general population. Having a more optimistic outlook on clinical trials also leads to greater likelihood of enrolling.[51]

Why do we conduct clinical trials?

The following reasons have been put forward:

- To allow medical professionals and patients to gain information about the benefits, side effects and possible uses of new drugs as well as new ways to use existing drugs
- To translate results of basic scientific research into better ways to prevent, diagnose, or treat a disease
- To know that any treatments we recommend are both safe and effective in humans
- To ascertain that cell culture and animal work can only take us so far!
- In areas of terminal diseases-
- Oncology, people are always looking for the miracle cure-and it is easy to get dragged into the idea. Trials are conducted for scientific, medical, evidence-based research paradigm

What happens in clinical study

Clinical research team check the health of the participant at the beginning of the trial. Pre-test Patient The evaluation gives specific instructions for participating in the trial and monitor the participant carefully during the trial, and stay in touch after the trial is completed. The tests Doctors' visits for Frequent follow up.

Who can participate in a clinical trial?

All clinical trials have guidelines about who can participate, exclusion/inclusion criteria can help produce reliable results. Criteria based on factors such as age/gender, type and stage of disease, prevention treatment and medical conditions are major factors in participation in a trial.

Do many people participate in a clinical trial?

Less than 5% of Adults patients participate in clinical trials, about 15% of healthy volunteers take part in CT. Only about 2% Pediatrics CT takes place in investigating new drugs.[44]

What are the barriers to participate in a Clinical trial studies?

The main barriers to participate in a clinical trial are as follows

- ✓ Physicians and other health professionals may be unaware of appropriate trials, and be unwilling to lose control of patient's care.
- ✓ The believe that standard therapy is best, and that clinical trials are more work,
- ✓ Have concerns about the patient's care or how the person will react to suggestion of clinical trial participation,
- ✓ Patients may be unaware of clinical trials taking place in their locality,
- ✓ Lack of access to trials, fear, distrust, or be suspicious of research
- ✓ Have practical or personal obstacles, and unwilling to go against their physicians' wishes

What are the Benefits of participating in a clinical trial?

Clinical trials at a minimum offers the best standard treatment Participants gain early access to new treatments. When the new treatment or intervention is proven to work, patients may be among the first to benefit. Participant are privileged to participation in advancing medical knowledge. Patients have a chance to help others and improve disease care-terminal diseases Participation is to play an active role in own health care. The medical team conducting the trial will carefully and regularly monitor the patient's progress.

Risk of participating in a Clinical trial?

Some participants argue that new treatments or interventions under study are not always better than, or even as good as standard care. In addition, even if a new treatment has benefits, it may not work for every patient and can cause unpleasant, serious or even life-threatening side effects. Clinical trials may require more time and attention than a non-protocol treatment.

Howa are patients right protected in a clinical trial?

Ethical and legal codes that govern medical practice also apply to clinical trials, Informed consent, Review boards. Scientific review, institutional review boards (IRBs), Data safety and monitoring boards.

Informed consent is a process/document designed to inform the patient of the purpose and design of a clinical study, possible side effects and benefits and if there are any other options. It should also include information on Voluntary participation, Duration of trial. Insurance and compensation, Name and phone number of contact person, procedures, Individual rights and confidentiality,

The Scientific review, Panel of experts Institutional review boards (IRBs), qualified people are there to evaluate new and ongoing trials All institutions that conduct clinical trials must, by law, have a IRB that approves the protocol Data and safety monitoring boards: Ensure that risks are minimized, Ensure data integrity, Stop a trial if safety concerns arise or objectives have been met

How can we tell clinical trials are conducted with the international norms and standards?

Studies are done in adherence to the Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects, CIOMS guidelines-Council for International Organizations of Medical Sciences, (CIOMS) in collaboration with the World Health Organization (WHO) Guide of Biomedical Research.GCP guidelines, Transparency and good communication, Use of Institutional Ethics committees, Capacity Building/ training of CT team on GCP, Ethical principles, CT Monitoring-Mandatory for Ethically approved Clinical Trials.

What can I do personally if I have an idea of a Clinical Trial?

What do you consider as the question you want to answer, then write a draft protocol, Decide if it is a phase I, II, III or pilot study, Write the Ethics Committee application, Clinical trials facilities/centres. A wide variety of clinical trials are performed in centres specialized in conducting CT. These include phase I/II and III studies of new drugs, and ongoing program in supportive care and psychosocial research. There are organization known as Clinical Research organization that handles CTs. Submit that Work out where funding will come from. Clinical trials are classified by the research objective created by the investigators.

Who are involved in clinical trials?

Clinical trials involve people who are ill (patients) to test new treatments, new combinations of drugs or new approaches to surgery or radiotherapy. Determine the most effective treatment for people who have a disease. Test safety and effectiveness of new agents or interventions in people with a disease condition. The sponsors, stakeholders, scientists, regulatory authorities and ethics committee are all involved in clinical trials good governance.

CONCLUSION

For patients to have access to the most effective and safest therapies possible, it is important to understand the key concepts involved in performing clinical trials. Understanding the ethical principles and regulations behind trial designs may also help key stakeholders respond to future clinical research challenges. A well-designed and executed clinical trials can contribute significantly to the national effort to improve the effectiveness and efficiency of global health care. Through rigorous practices applied to novel drug development and approval, physicians and patients can maintain confidence in the therapies prescribed. To ensure the safety of subjects who volunteer for clinical trials as well as preserving the integrity and credibility of

the data reported, numerous regulatory boards including IRBs and DSMBs are involved. The rigorous methodology of executing a clinical trial, most significantly through the controlled and random intervention of human volunteers by the investigator, makes epidemiologic study design one of the most powerful approaches to demonstrating causal associations in the practice of evidence-based medicine. By emphasizing safety first, the most common route of studying a new therapeutic is from the establishment of the maximum tolerated dose in humans (phase I), to pharmacodynamic and pharmacokinetic studies, and exploration of therapeutic benefit (phase II), followed by comparing its efficacy to an established therapeutic or control in a larger population of volunteers (phase III), and ultimately post-market evaluation of adverse reactions and effectiveness when administered to the general population (phase IV).

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AUTHORS CONTRIBUTION

CNF, ETF designed the study. Authors LBF, JDF and NCK did data mining/case studies. All authors read and approved final draft.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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