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CLINICAL TRIALS: A GENERAL REVIEW

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ABSTRACT

Developers of drugs, biologicals and medical devices must assure product safety, exhibit medical benefit in people and mass produce the product. Pre-symptomatic studies show that safety and effective. Clinical trial phases are steps in the research to determine if an interference would be beneficial (or) detrimental to human's and includes phases 0,1,2,3,4 and 5 clinical studies. Awareness on the basis of clinical trial researches plan and implement clinical study protocol and by doing so, improve the number of therapies coming to market for patients. Clinical trials are the mandatory for leading newer and preferred drugs to market in today's global scientific era. Clinical trials test probable treatments in human's volunteers which are extensively used in general population.In phase-1pharmacokinetics,safety,gross,consequences are studied on human volunteer's .If the drug passes the test ,it enters phase-2 testing ,where pharmacokinetics ,safety,therapeutic efficiency are studied on selected patient's by clinical pharmacologist ,if passes hundreds of selected patients are now studied ,primarily for safety and therapeutical effectiveness by clinical investigators in phase-3.If phase-3 is passed the drug is now approved and marketed efficacy in phase-4.Manuscript abstracts represent critical source of information for oncology practioners.Gain intensified health care for a article diseases (or) health condition. There may be fewer side effects compared the standard treatment. The study treatment on medicine may not make you feel better.There may be more side effects compared to standard treatment. Clinical trials results are often interpreted by generalization, in a trial design-limited manner, directed towards moderation of the current clinical practice.

INTRODUCTION

A clinical trial is a research study that tests a new medical treatment or a new way of using an existing treatment to see if it will be a better way to prevent and screen for diagnose or treat a disease[1]. For any new drug to enter in clinical trial, it must pass preclinical studies. Preclinical studies involve in vitro (i.e., test-tube or Laboratory) studies and trials on animal populations. Wide range of dosages of the study drug is given to animal subjects or to an in-vitro substrate in order to obtain preliminary efficacy, toxicity and pharmacokinetic information[2]. In the United States, the Food and Drug Administration (FDA) approves new drug products for sale and marketing based on results from clinical investigations that demonstrate the safety and efficacy of a drug for a proposed indication. Sponsors of a drug (e.g., companies, research institutions, or government) seek approval by submitting a new drug application (NDA)to the FDA, which must include documentation and analyses of all animal and human trial data, as well as information about the ingredients, clinical pharmacology, manufacturing, processing, and packaging of the drug. The FDA relies on sponsors to

submit all data, including complete protocols, protocol revisions, and data from failed trials in the NDA. The NDA is then reviewed by clinicians, statisticians, chemists, clinical pharmacologists, and other relevant scientific and regulatory disciplines within the FDA to confirm and validate the sponsor's conclusion that a drug is safe and effective.

NEED OFCLINICALTRIALS

Many clinical trials are done to see if a new drug or device is safe and effective for people to use. Clinical trials are also done for other reasons. Some compare existing treatments to determine which is better. The current, approved treatments are called the "standard treatments". Sometimes clinical trials are used to study different ways to use, and/or decrease side effects. Sometimes, studies are done to learn how to best use the treatment in a different population, such as children, in whom the treatment was not previously tested.For most trials, researchers, doctors, and other health professionals administer the clinical trials according to strict rules set by the food and drug administration (FDA). FDA sets the rules to make sure that people who agree to be in studies are treated as safely as possible.Clinical trials can be classified in to various ways One way is to classify clinical trials on basis of mode of the study.

TYPES OF CLINICAL TRIALS

1) Interventional Study: -in this study researchers measure how the subjects' health changes. They give the research subjects a particular medicine and then compare the treated subjects with those receiving no treatment or the standard treatment. This is a type of a comparative study.

2) Clinical observational study: - in this study the researchers observe the subjects given with new medicine and measure their outcomes. Another way is to classify trials is by their purpose.

• **Prevention trials** to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes.

• **Screening trials** test the best way to detect certain diseases or health conditions.

• **Diagnostic trials** are conducted to find better tests or procedures for diagnosing a particular disease or condition.

• **Treatment trials** test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.

• **Quality of life trials** (supportive care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness.

• **Compassionate use trials or expanded access trials** provide partially tested, unapproved therapeutics to a small number of patients who have no other realistic options. 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.

CLASSIFICATION OF CLINICAL TRIALS

Phase I trials are often small studies designed to provide supporting information about a drug's pharmacokinetic parameters, dosing schedule, common side effects, tolerability, and toxicity, but are limited by design or other factors in their ability to demonstrate efficacy. Phase II and III trials are often larger studies designed to provide evidence on the overall risks and benefits of a drug. The phase of a trial was often not reported in the FDA documents. Sponsors and the FDA frequently categorize certain trials as ''pivotal.'' These are trials that demonstrate the efficacy and safety of a drug for its proposed indication and provide the most useful information for clinical decision-making. Pivotal trials are typically Phase II or III trials, but there is no formal definition of a pivotal trial. In practice, trials that are reported in the ''clinical studies'' or ''clinical efficacy'' section of the FDAapproved drug label are considered pivotal. We used this scheme to categorize trials as ''pivotal'' or ''nonpivotal.'' We obtained the product label at the time of FDA approval for each new drug, or the next available product label if the initial product label was not available, at http://www.fda.gov/ cder/approval/index.htm. Trials described in the summary documents for each drug approval that were also

described in the ‘‘clinical studies’’ section of the corresponding drug label were categorized as pivotal. All other trials were categorized as nonpivotal.

PHASES OF CLINICAL TRIALS

1. Phase 0 Clinical Trials: In September 2003, the National Institutes of Health (NIH) announced a series of initiatives to address the growing crisis in moving new basic science discoveries to the market where they are available for patient use. One of the objectives was strengthening clinical research infrastructure**[6]**. This was followed by an FDA report issued in March 2004 analysing the “Challenge and Opportunity on the Critical Path to New MedicalProducts”**[7]**. US Pharmaceutical R & D Spending and the NIH Budget had increased dramatically between 1993 and 2003, but major drug and biological product submissions to the FDA decreased. Investment required for one successful drug launch increased from $1.1B in 1995-2000 to $1.7B in 2000-2002. The critical path, which begins when candidate products are selected for development, was challenging, inefficient, and costly.Clinical failure included safety problems and lack of effectiveness. The concern was stagnation and declining innovation with a widening gap between knowledge and clinical use. A drug entering Phase I trials in 2000 was not more likely to come to market than one entering Phase I trials in 1985 **[8]**. Improvement in prediction of failure during early clinical trials saves in development costs and time to market **[9]**. The concept of exploratory investigation new drug (IND) studies was a result of this FDA analysis and can help with determining whether a defined mechanism of action can also be observed in humans, provide information on pharmacokinetics, select promising products from a group of candidates, and evaluate biodistribution. The purpose of these studies is to help in the go versus no-go decision-making process of a drug’s fate early in the development process using human models rather than relying on animal data.Exploratory IND studies (also known as Phase 0 studies) are conducted early in clinical phase studies and involve limited human exposure and have no therapeutic or diagnostic intent. Doses are subtherapeutic and patients are monitored by the clinical researcher and involve about 10 study patients. Duration of a patient’s participation is usually less than 1 week. Pharmacodynamics and pharmacokinetics are studied. These trials are before the traditional dose escalation, safety, and tolerance studies, do not replace the Phase I clinical trials and do not indicate whether a therapy has a positive impact on the targeted pathology. These studies help in eliminating candidate therapies before they reach Phase I studies **[10]-[12]**. These trials were developed to shorten the critical path for drug development, to explore pharmacokinetic and pharmacodynamic profiles of INDs in humans, to help in accelerating identification of promising drugs, and to reduce development time and costs. Limitations of these trials include lack of therapeutic intent, motivation of patients to participate, may delay or exclude patients from other clinical trials that may have therapeutic intent, micro-dosing pharmacokinetics and relationship to therapeutic dose, and availability of sensitive analytical methods **[13]**. Attrition rates are high and only about 8% come to market.

2. Phase I Clinical Trials

A Phase I clinical trial evaluates the best way to administer a drug, its frequency and dose, the maximum tolerated dose (MTD), and side effects. Tolerability, pharmacokinetics, and pharmacodynamics are evaluated. These studies determine, most importantly, if the treatment is safe. Trials usually include 20 to 100 patients and are monitored by the clinical researcher. Doses are increased if there are no severe side effects and patients are tested to determine if he or she is responding to the therapy. These escalation dose studies are used to determine the best and safest dose that can be administered and is a fraction of the dose that caused harm during animal testing. Unnecessary exposure of subjects to subtherapeutic doses while maintaining safety and rapid accrual is the primary goal of Phase I trials **[14]**. Subjects, in most cases, are healthy volunteers although patients with a certain disease may be required. Contract research organizations usually conduct these studies and stipends may be given. Testing is usually sequential with data being reviewed

after every patient or small group of patients.Dose-toxicity and dose-efficacy curves are determined during this phase and include single ascending dose trials (Phase IA), multiple ascending dose trials (Phase IB), and food effect studies. Dose escalation methods dose-toxicity curve and allow escalation and de-escalation of the dose with diminishing fractions of the preceding dose depending on presence or absence of toxicity. They are easy to implement and do not require special software. The traditional 3 + 3 design proceeds with cohorts of 3 patients. The starting dose is based on extrapolation from animal toxicological data. Increasing dose levels have been fixed in advance and usually follow a modified Fibonacci sequence in which the dosing increments become smaller as the dose increases **[15].** If none of the patients experience a dose-limiting toxicity, 3 more patients will be treated at the next higher dose. If 1 of the patients experiences a dose-limiting toxicity, the same dose is repeated in 3 more patients. Dose escalation continues until at lease 2 patients from a cohort of 3 to 6 experience dose-limiting toxicities. Recommended dose for Phase II trials is defined as the dose level just below the toxic dose level.Alternate rule-based dose escalation methods include the "2 + 4," "3 + 3 + 3," and "3 + 1 + 1" ("best of five") rules **[16].** study, a third cohort of 3 patients is added if 2 of 6 patients in the first 2 cohorts have a dose-limiting toxicity. If at least 3 of 9 patients experience a dose-limiting toxicity, the study is terminated. The "best of 5" design requires that 1 additional patient is added if 1 or 2 dose-limiting toxicities are observed in the first 3 patients.Another patient is added if 2 dose-limiting toxicities are seen among the 4 treated patients. Escalation is continued if no dose-limiting toxicities are seen of 3, 1 of 4, or 2 of 5 patients. If 3 or more dose-limiting toxicities are seen, the trial is stopped.Accelerated titration designs combine variations of the 3 + 3 design and the model-based design. Patient assignment to doses is based on prespecified rules. Pharmacologically guided dose escalation is a variation of the 3 + 3 design method. This assumes that animal model studies accurately reflect dose-limiting toxicities based on plasma drug concentrations. In the first stage, plasma exposure is extrapolated from preclinical data. Pharmacokinetic data are then obtained for each patient to determine subsequent dosing **[17].** The isotonic regression model assumes toxicity is nondecreasing with dose and fits an isotonic regression to accumulated data. The dose given is that with estimated toxicity thought closest to the maximum tolerable toxicity **[18].** The "rolling six designs" allows for accrual of 2 to 6 patients concurrently onto a dose level based on the number of patients enrolled and evaluable, the number having dose-limiting toxicity (DLT), and the number still at risk of developing DLT **[19].** This design is intended to shorten the study duration in which there is prior information about the dose range and is useful in paediatric populations. The "biased coin up-and-down design" requires that the treatment response or the toxicity evaluation is observed quickly, allocates a dose to each patient based on the toxicity information of the last completed subject and allows multiple patients to be concurrently studied **[20]-[22].**Another rule-based design allows subsequent patients to be assigned to doses according to the toxicity outcomes at the current dose by calculating the toxicity probability interval under the beta-binomial model **[23].**

3. Phase II Clinical Trials: Phase I/II dose finding studies determine the most successful dose (MSD) which is the dose which maximizes the product of the probability of seeing no toxicity together with the probability of seeing a therapeutic response.While a Phase I clinical study focuses on determining the MTD, Phase II studies evaluate potential efficacy and characterizes treatment benefit for the disease in a convincing manner. The intervention is not presumed to have any therapeutic effect whatsoever. These studies are performed on larger groups (100 to 300 subjects) and are designed to assess how well the drug works and to continue safety assessments. Therapeutic doses which were determined during Phase I are administered and patients are monitored by the clinical researcher.

Trials are often conducted in a multi-institution setting. Phase II may be divided into Phase IIA which are pilot clinical trials to evaluate efficacy and safety in selected populations with the disease or condition to be treated, diagnosed or prevented (objectives may be on dose-response, type of patient, frequency of dosing, or other identifiers of safety and efficacy) and Phase IIB which are the most rigorous trials designed to demonstrate efficacy. The development process usually fails during this Phase II when the drug is discovered not to work as planned or to have toxic effects.The Phase II design depends on the quality and adequacy of Phase I studies. A vulnerable aspect of both phases is the type of patient enrolled. Patients in Phase II trials generally have more exclusion criteria than those in Phase III trials. Case series and randomized clinical trial designs have been used. Single stage and multi-stage Phase II clinical trial designs are often developed on the basis that one endpoint is of interest. A commonly used Phase II design is based on the work of Gehan, a version of a two-stage design **[24].** Other designs have more stages or a sequential aspect. Hybrid designs have been used to improve efficiency. In an update, Gehan reviewed statistical aspects of plans for Phase II cancer clinical trials including a minimum number of patients plan, a two-stage decision theory approach, a limited patient accrual plan, a predictive probability plan, and a one-sample multiple testing procedure plan. The author makes recommendations regarding the plan that best fits the needs of the study **[25].**

4. Phase III Clinical Trials: Phase III trials are the full-scale evaluation of treatment and are designed to compare efficacy of the new treatment with the standard treatment. These are the most rigorous and extensive type of scientific clinical investigation of a new treatment. This is the "pre-marketing phase" of clinical trials. These are usually the most expensive and time-consuming of the trials. The trials may be difficult to design and run. Large groups (100 to 3000 subjects) are recruited and trial designs have included randomized controlled trials (parallel design), uncontrolled trials (single treatment), historical controls, no-randomized concurrent trials, factorial designs, and group sequential designs. Patients are monitored by the clinical researcher and personal physician. Phase III clinical trials may be divided into Phase IIIA which are trials done after efficacy of the therapy is demonstrated but before regulatory submission of a New Drug Application (NDA) or other dossier and Phase IIIB which are conducted after submission of an NDA or other dossier but before approval and launch.During the 1980's, the FDA published guidance documents that efficacy should be demonstrated by prolongation of life, improved health-related quality of life, or an established surrogate for one of these. If the new therapy results in a statistically significant improvement, the new treatment is usually approved for clinical use **[26].**The European Organisation for Research and Treatment of Cancer recognize that these designs can be advantageous, but warn that they must prevent bias that could be uncontrollable. Recommended techniques include randomisation, blinding, prospectively planned adaptations and upfront implementation of the process and firewalls needed to ensure restricted access to interim analysis results and blinding of staff involved in day-to-day trial proceedings **[27].**

5. Phase IV Clinical Trials: Upon authorization by the FDA, therapies determined to have proven safety, efficacy and quality may be made available to the general population. Patients and their physicians have expectations of benefit. However, not all safety or efficacy issues have been determined. The FDA requires continued evaluation after release to evaluate safety signs that may affect the benefit-risk ratio **[27] [28].**These Phase IV studies include "all studies (other than routine surveillance) performed after drug approval and related to the approved indication" **[29].**These are post-marketing surveillance studies. The focus of the trials is on how drugs work in the real world. Anyone seeking treatment from their physician may be treated with the therapy. Their personal physician monitors the results of treatment. Efficacy and detection of rare or long-term adverse effects over a much larger patient population and longer time period are evaluated, healthcare costs and outcomes are

determined, and pharmacogenetics are studied. New clinical indications for a drug may be established and large number of patients and physicians are involved**.** The FDA may require that a developer conduct a Phase IV trial as a stipulation for drug approval. Less than half of studies are completed or even initiated by developers **[30].**Phase IV trials may result in a drug being removed from the market or restricted to certain indications.Initially, these trials were run much like Phase III studies and were conducted for marketing purposes. Studies were done at institutions with investigators familiar with clinical trials and had inclusion and exclusion criteria similar to those of Phase III studies. Results did not reflect what would happen under normal conditions. As a result, innovative studies were designed to involve ordinary physicians in naive research communities. Goals have been broadened and include evaluation of specific pharmacological effects, establishing the incidence of adverse reactions, determining effects of long-term administration of a therapy, establishing a new clinical indication for the therapy, evaluation of the therapy in higher risk populations, etc. A main issue of concern is the mix of medical research and clinical practice **[31].**Reported serious adverse drug reactions submitted to the FDA's Med Watch program have increased from 150,000 in 2000 to 370,000 in 2009 **[32].**Physician and consumers or drug manufacturers submit these reports.Criticisms have included reliance on voluntary reporting of adverse events, trust in drug manufacturers to collect/evaluate/report drug safety data that may risk financial interests, and dependence on one government body Proffered solutions have included large-scale simple RCTs with few eligibility and treatment criteria **[33],**pre-planned meta-analyses of a series of related trials**[34],**and establishment of a national health data network to evaluate post-marketing surveillance independent of the FDA-approval process **[35].**

IDENTIFICATION OF CLINICAL TRIALS: We identified all drugs approved by the FDA between January 1998 and December 2000 at the Centre for Drug Evaluation and Research Web site, available at http://www.fda. gov/cder/da/da.htm. We included only new drugs classified as ‘‘new molecular entities,’’ which are drug products that have never been previously approved by the FDA for any indication, hereafter referred to as ‘‘new drug.’’ For each new drug, we retrieved the FDA Summary Basis for Approval and evaluated the medical and statistical review documents to identify clinical trials submitted by the sponsor. These review documents are available at http://www.accessdata.fda.gov/ scripts/cder/drugsatfda/index.cfm for all new drugs approved since 1998.

MONITORING CLINICAL TRIALS: The purposes of trial monitoring are to verify that: The rights and well-being of human subjects are protected. The reported trial data are protected. The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

ETHICAL CONSIDERATION: An Independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non- medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by among other things, reviewing and approving /providing favourable opinion on, the trial protocol, the suitability of the investigators facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the independent Ethics Committee to act in agreement with GCP as described in this guideline.

DEVELOPMENT OF CLINICAL TRIALS: The first clinical trial of a novel therapy was conducted unintentionally by the Renaissance surgeon Ambroise Pare in 1537. He used aconcoction of turpentine, rose oil and egg yolk to prevent the infection of battlefield wounds, noting that the new treatment was much more effective that the

traditional formula. James Lind documented the fact that citrus fruits in the diet could prevent scurvy. From 1800 onwards, clinical trials began to proliferate and more attention was paid to study design. Placebos were first used in 1863, and the idea of randomization was introduced in 1923. The first trial using properly randomized treatment and control groups was carried out in 1948 by the Medical Research Council, and involved the use of streptomycin to treat pulmonary tuberculosis. Information flowing from the clinical research enterprise directly influences over the cost, quality, and efficiency of our health care system. The pressure for our clinical research enterprise to produce high quality information and to speed the translation of advances from basic science to clinical care, and then to better health, will continue to grow [9]. Even more serious is the lack of confidentiality. Unlike China, India does not yet grant protection for data gleaned from clinical trials, which makes it easy for generic drug makers to copy the drug under trial. Under India's existing laws, only those drugs that have already passed Phase 1 safety trials in the country of their origin can be tested on Indians. In India, opportunities will become limited unless there is a very strong patent law and mechanism to enforce it. Drafting patent laws with the help of industry experts and its implementation is highly essential.

CLINICAL TRIALS IN INDIA: India is looked upon as a favourable destination for conducting global clinical trials. It is estimated that nearly 20% of all global clinical trials are conducted in India. Being the second largest populated country in the world, India can contribute significantly to global drug development programs. India provides an opportunity in terms of availability of large patient populations, highly educated talent, a wide spectrum of disease, lower costs of operations,low cost of medication compared to other developed countries and a favourable economic, intellectual property environment, and importantly, use of English as the primary language make it easy to set up clinical sites in India. India's equivalent to the US Food and Drug Administration (FDA) and European Medicines Agency (EMEA) is the office of the Drugs Controller General (India) (DCGI). The DCGI is the federal official responsible for all pharmaceutical related issues in India. The DCGI is equivalent to the commissioner of FDA. India follows schedule Y for drug trials and Schedule Y is equivalent to the IND regulations 21CFR:312. In India, DCGI is not subdivided into several centres and offices to individually regulate different kinds of products. but, the DCGI himself signs on all applications filed with his office. These include not only clinical trial applications but all applications for marketing approval of drugs and medical devices, for import and export of regulated products and for manufacturing. India follows ICH E6 guidance for clinical trials7-9. The Indian Council of Medical Research (ICMR) released an Indian version of GCPs to for India specific issues for conducting clinical operations. An IEC in India is similar to an Institutional Review Board (IRB) in the US. All sites need to have IEC approval, in addition to the DCGI's approval, before enrolling any subject. In India clinical trial application process takes about 4-8 weeks for starting a trial, while in US, other European countries and Australia, it takes about 2-4 weeks for processing an application fortrial.

CONCLUSION

A clinical trial is compulsory for a drug/device to ensure its safety and efficacy in humans before their usage. It involves 1-4 with specific objectives and end results. Clinical trials must follow guidelines and protocols to ensure well being of participants. India have undergone many changes from 2008 to till date, still altering. These changes made India to be a global hub for clinical trials. Being the second most populated country in the world, India can contribute significantly to global drug development programmes.

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