



## CLINICAL TRIAL AND DATA MANAGEMENT

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### ABSTRACT

Clinical trials are the process by which a new drug's safety and effectiveness are tested as part of the FDA approval process. When a company discovers and develops a new drug, they must first run extensive pre-clinical trials prior to testing the drug candidate on people. Clinical trials that are well-designed and well-executed are the best approach for eligible participants to play an active role in their own health care and Gain access to new research treatments before they are widely available. Management of data in clinical trials is a valuable work for anyone involved in any type of clinical trial, from large multicenter trials to small single-investigator studies.

**Keywords:** Clinical trials, Data management, Clinical studies.

### INTRODUCTION

Clinical trials are also called clinical studies, research protocols or medical research and often compare one drug against another to see which is more effective, or the medicine or procedure in a specific demographic group or for a specific disease. Clinical trials are designed to help find out how to give a new treatment safely and effectively to people. New therapies are designed to take advantage of what has worked in the past and to improve on this base. There are certain steps and protocols, which needed to be followed while carrying out the actual clinical trials. Treatments now being used (standard treatments) are the base for building new, hopefully better, treatments<sup>1,2</sup>. The pharmaceutical industry is the main sponsor of medicines research in the UK. Sponsors have to demonstrate the safety, quality and efficacy of a potential new medicine – called an investigational medicinal product (IMP) – through a series of rigorous trials in humans in order to obtain a license, so that doctors can give the medicine to patients. But before an IMP can be given to humans, sponsors must first test it thoroughly in animals. The main aims of these pre-clinical studies are:

- to find out the effects of the IMP on body systems (pharmacodynamics);
- to study the blood levels of the IMP, and how it is absorbed, distributed, metabolised and eliminated after dosing (pharmacokinetics);
- to find out if a range of doses of the IMP, up to many times higher than those intended for use in humans, are toxic to animals<sup>10</sup> and if so, to identify the target organs and the margin of safety in terms of (a) the no observed-adverse-effect dose level (NOAEL) relative to body weight and (b) IMP exposure - the concentration of the IMP in the bloodstream over 24 hours (toxicokinetics)<sup>3</sup>. and

- to make a formulation of the IMP, such as a capsule or injection, suitable for early studies in humans.

After the pre-clinical studies, there are four phases of trials in humans, which in practice often overlap. Phases 1 to 3 are done before a license is granted and phase 4 is done after authorisation<sup>4</sup>.

### DEFINITION

The broad definition of clinical trial includes definitions allowing for use of the term in references to studies involving a single treatment (e.g. as in most Phase I trials and some Phase II drug trials) and for studies involving use of an external control (e.g. studies involving historical controls) The treatment can be anything considered to hold promise in caring for the sick, in the prevention of disease, or in the maintenance of health<sup>5</sup>. The National Library of Medicine defined a clinical trial in 1980 as: a pre-planned, usually controlled trial of the safety, efficacy, or optimum dosage schedule of one or more diagnostic, therapeutic, or prophylactic drugs or techniques in humans selected according to predetermined criteria of eligibility and observed for predefined evidence of favourable and unfavourable effects.

### REGULATIONS FOR CLINICAL TRIALS

Clinical trials are closely supervised by appropriate regulatory authorities. All studies that involve a medical or therapeutic intervention on patients must be approved by a supervising ethics committee before permission is granted to run the trial. The local ethics committee has discretion on how it will supervise non interventional studies (observational studies or those using already collected data). In recent years, there have been many changes to the regulatory aspects of clinical trials. Most changes stem from the introduction of Good Clinical Practice (GCP), Good Manufacturing Practice (GMP) and



the Clinical Trials Directive, which is based on GCP and GMP.

Clinical research regulation in different countries are-

- In Australia:- Therapeutic Goods Administration (TGA)
- In Europe:- The European Agency for the Evaluation of Medicinal Product (EMA)
- In UK:- Medicines and Healthcare products Regulatory Agency (MHRA)
- In India:- Drug Controller General of India (DCGI)

#### Clinical Trials Guidelines in India:

The guidelines that govern the conduct of Clinical Trials in India include:

- Schedule Y of drugs and Cosmetics Act, 1940
- Ethical Guidelines for Biochemical Research on Human Subjects
- Good Clinical Practice, 2001

### PHASES OF CLINICAL TRIALS

Before pharmaceutical companies start clinical trials on a drug, they conduct extensive pre-clinical studies. Pre-clinical studies involve in vitro (i.e., test tube or laboratory) studies and trials on animal populations (in vivo). Wide-ranging dosages of the study drug are given to the animal subjects or to an in-vitro substrate in order to obtain preliminary efficacy, toxicity and pharmacokinetic information and to assist pharmaceutical companies in deciding whether it is worthwhile to go ahead with further testing. Clinical trials involving new drugs are commonly classified into four phases. Each phase of the drug approval process is treated as a separate clinical trial. The drug-development process will normally proceed through all four phases (Table 1) over many years. 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. Phase IV are 'post-approval' studies.

**Table 1:** Different phases of clinical trials

Phase	Phase I	Phase II	Phase III	Phase IV
<b>Objectives</b>	Determine the metabolic and pharmacological actions and the maximally tolerated dose	Evaluate effectiveness, determine the short-term side effects and identify common risks for a specific population and disease	Obtain additional information about the effectiveness of clinical outcomes and evaluate the overall risk-benefit ratio in a demographically diverse sample	Monitor ongoing safety in large populations and identify additional uses of the agent that might be approved by the FDA
<b>Factors to be identified</b>	-Bioavailability -Bioequivalence -Dose proportionality -Metabolism -Pharmacodynamics -Pharmacokinetics	-Bioavailability -Drug-disease interactions -Drug-drug interactions -Efficacy at various doses -Pharmacodynamics -Pharmacokinetics -Patient safety	-Drug-disease interactions -Drug-drug interactions -Dosage intervals -Risk-benefit information -Efficacy and safety for subgroups	-Epidemiological data -Efficacy and safety within large, diverse populations -Pharmacoeconomics
<b>Data focus</b>	-Vital signs -Plasma and serum levels -Adverse events	-Dose response and tolerance -Adverse events -Efficacy	-Laboratory data -Efficacy -Adverse events	-Efficacy -Pharmacoeconomics -Epidemiology -Adverse events
<b>Design features</b>	-Single, ascending dose tiers -Unblinded -Uncontrolled	-Placebo controlled comparisons -Active controlled comparisons -Well-defined entry criteria	-Randomized -Controlled -2-3 treatment arms -Broader eligibility criteria	-Uncontrolled -Observational
<b>Duration</b>	Up to one month	Several month	Several years	Ongoing (following FDA approval)
<b>Population</b>	Healthy volunteers or individuals with the target disease (such as cancer or HIV)	Individuals with target disease	Individuals with target disease	Individuals with target disease, as well as new age groups, genders, etc.
<b>Sample size</b>	20 to 80	200 to 300	Hundreds to thousands	Thousands



## Phase 0

Phase 0 is a recent designation for exploratory, first-in-human trials conducted in accordance with the U.S. Food and Drug Administration's (FDA) 2006 Guidance on Exploratory Investigational New Drug (IND) Studies<sup>6</sup>. Phase 0 trials are also known as human micro dosing studies and are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in human subjects as was anticipated from preclinical studies. Distinctive features of Phase 0 trials include the administration of single sub therapeutic doses of the study drug to a small number of subjects (10 to 15) together preliminary data on the agent's pharmacokinetics (how the body processes the drug) and pharmacodynamics (how the drug works in the body). A Phase 0 study gives no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect. Drug development companies carry out Phase 0 studies to rank drug candidates in order to decide which has the best PK parameters in humans to take forward into further development.

## Phase I

Phase I Trial Address:

- How rapidly the drug is absorbed?
- Where is the drug distributed in the body?
- Which organ systems are involved in metabolism of the drug?
- How quickly is the drug eliminated from the body?

Phase I trials are the first stage of testing in human subjects. Normally, a small (20-80) group of healthy volunteers will be selected. This phase includes trials designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug. These trials are often conducted in an inpatient clinic, where the subject can be observed by full-time staff. The subject who receives the drug is usually observed until several half-lives of the drug have passed. Phase I trials also normally include dose-ranging, also called dose escalation, studies so that the appropriate dose for therapeutic use can be found. Phase I trials most often include healthy volunteers. However, there are some circumstances when real patients are used, such as patients who have end-stage disease and lack other treatment options. This exception to the rule most often occurs in oncology (cancer) and HIV drug trials. Volunteers are paid an inconvenience fee for their time spent in the volunteer centre. There are different kinds of Phase I trials:

### SAD

Single Ascending Dose studies are those in which small groups of subjects are given a single dose of the drug while they are observed and tested for a period of time. If they do not exhibit any adverse side effects, and the pharmacokinetic data is roughly in

line with predicted safe values, the dose is escalated, and a new group of subjects is then given a higher dose. This is continued until pre-calculated pharmacokinetic safety levels are reached, or intolerable side effects start showing up (at which point the drug is said to have reached the Maximum tolerated dose (MTD).

### MAD

Multiple Ascending Dose studies are conducted to better understand the pharmacokinetics & pharmacodynamics of multiple doses of the drug. In these studies, a group of patients receives multiple low doses of the drug, whilst samples (of blood, and other fluids) are collected at various time points and analyzed to understand how the drug is processed within the body. The dose is subsequently escalated for further groups, up to a predetermined level.

### Food effect

A short trial designed to investigate any differences in absorption of the drug by the body, caused by eating before the drug is given. These studies are usually run as a crossover study, with volunteers being given two identical doses of the drug on different occasions; one while fasted, and one after being fed.

## Phase II

Phase II Trial Address-

- What is the minimum effective dose?
- What is the maximum tolerated effective dose?
- Is the drug effective in mild, moderate and severe cases of the disease or condition?
- Is the drug effective for all expected indications?

Once the initial safety of the study drug has been confirmed in Phase I trials, Phase II trials are performed on larger groups (200-300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments in a larger group of volunteers and patients. When the development process for a new drug fails, this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects. Phase II studies are sometimes divided into Phase IIA and Phase IIB. Phase IIA is specifically designed to assess dosing requirements (how much drug should be given), whereas Phase IIB is specifically designed to study efficacy (how well the drug works at the prescribed dose(s)). Some trials combine Phase I and Phase II, and test both efficacy and toxicity.

## Phase III

Phase III Trial Address:

- Overall benefit-risk relationship
- Adverse in a large group of patient over a longer period of exposure



- The ideal dosage regimen
- Should the drug is allowed to be marketed?

Phase III studies are randomized controlled multicenter trials on large patient groups (300–3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment. Because of their size and comparatively long duration, Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions. It is common practice that certain Phase III trials will continue while the regulatory submission is pending at the appropriate regulatory agency. This allows patients to continue to receive possibly lifesaving drugs until the drug can be obtained by purchase. Other reasons for performing trials at this stage include attempts by the sponsor at "label expansion" (to show the drug works for additional types of patients/diseases beyond the original use for which the drug was approved for marketing), to obtain additional safety data, or to support marketing claims for the drug. Studies in this phase are by some companies categorized as "Phase IIIB studies"<sup>7,8</sup>.

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

#### Phase IV

Phase IV trial is also known as Post Marketing Surveillance Trial. Phase IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold. Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I-III clinical trials<sup>9</sup>.

#### Randomized Trial

A *randomized trial* is a trial having a parallel treatment design in which treatment assignment for persons (treatment units) enrolled is determined by a randomization process. The trialist's purpose in randomization is to avoid selection bias in the formation of the treatment groups. The bias is avoided because the treatment to which a person is assigned is determined by

a process not subject to control or influence of the person being enrolled or those responsible for recruiting and enrolling the person<sup>10</sup>.

The randomization may be simple (complete) or restricted. The purpose of restriction is to force the assignments to satisfy the specified assignment ratio at intervals during enrolment. The randomization also may be stratified. The purpose of stratification is to provide treatment groups comprised of persons or treatment units having identical (within the limits of the stratification) distributions of the stratification variable. It is useful only in so far as the variable used for stratification serves to influence or moderate the outcome of interest<sup>11</sup>.

There are two processes involved in randomizing patients to different interventions. First is choosing a randomization procedure to generate a random and unpredictable sequence of allocations. This may be a simple random assignment of patients to any of the groups at equal probabilities, or may be complex and adaptive. A second and more practical issue is allocation concealment, which refers to the stringent precautions taken to ensure that the group assignment of patients are not revealed to the study investigators prior to definitively allocating them to their respective groups. A randomized controlled trial (RCT) is a type of scientific experiment most commonly used in testing the efficacy or effectiveness of healthcare services (such as medicine or nursing) or health technologies (such as pharmaceuticals, medical devices or surgery). RCTs are also employed in other research areas, such as judicial, educational, and social research. As their name suggests, RCTs involve the random allocation of different interventions (treatments or conditions) to subjects. This ensures that both known and unknown confounding factors are evenly distributed between treatment groups<sup>12</sup>.

#### CLINICAL TRIAL AND DATA MANAGEMENT

Data management is one most critical areas in any clinical research protocol. Indeed, data are the most important product of clinical research; and the ability to store, manipulate, analyze and retrieve data is critical to the research process, data resulting from clinical trials, therefore, is one of the most valuable assets that an investigator, pharmaceutical company, or research institution has. The data collected in a clinical trial constitute an accounting of the trial. Rules and guidelines that govern research include the Code of Federal Regulations<sup>13</sup>, the Good Clinical Practices (GCPs) guidelines from the International Conference on Harmonisation, state laws, sponsor standard operating procedures (SOPs), and institutional SOPs. The GCPs are an international ethical and scientific quality standard for clinical trial conduct<sup>14</sup>. A trial conducted under good clinical practices is the basis for demonstrating that the trial was conducted according to protocol. Plans for data management should be set up early during the





development phase of a clinical trial. Included in the plan are the appropriate mix of research personnel and resources such as staff time, workspace, computer equipment, and secure storage facilities for both paper and electronic equipment.

### Research team

The research team consists of individuals who possess the expertise specific for the study. The number of members on the research team usually depends on the sample size of the clinical trial and whether the institution conducting the trial has a dedicated research department. They check the health of the participant at the beginning of the trial, give specific instructions for participating in the trial, monitor the participant carefully during the trial, and stay in touch after the trial is completed<sup>15</sup>. Research team includes:

1. Sponsor
2. Principal investigator
3. Co-investigator
4. Clinical trial nurse
5. Data manager
6. Statistician
7. Other

### Sponsor

A sponsor can be an individual, such as a physician, or an organization, such as a pharmaceutical company, an academic centre, or a government agency such as an institute or a centre. In some studies, the sponsor provides financial support. Responsibilities of sponsor are:

- Verification that regulatory issues are met
- Submission of an investigational new drug (IND) application to the Food and Drug Administration (FDA)
- Reporting of serious adverse events to the FDA
- Monitoring the study to verify that it is being conducted according to the approved protocol
- Informing investigators at all sites of significant new adverse events
- Selection of qualified investigators

### Principal investigator

A Principal Investigator (PI) is the physician who leads the conduct of a clinical trial. For clinical trials of investigational drugs sponsored by the pharmaceutical industry under FDA regulations, the Principal Investigator is the physician who is responsible for the study performed at a particular research location or site. The Principal Investigator, or PI, must sign an FDA Form 1572 prior to the start of each clinical trial, signifying acceptance of responsibility for all aspects of the clinical trial as listed on the form. In addition, the PI also agrees to conduct the trial according to the written protocol,

obtain approval of the institutional review board (IRB) prior to initiating the trial and at any time the protocol is amended, maintain adequate records of the trial, protect subjects through the informed consent process, and notify the sponsor and the IRB of adverse events. Generally, pharmaceutical companies carefully screen prospective physicians for prior research experience and training before allowing them to sign as Principal Investigator for a clinical trial. PI is responsible for ensuring that the trial is conducted according to good clinical practices. Main responsibilities of clinical investigator are:

- Follow the protocol carefully
- Obtaining ERB/IEC/IRB approval to conduct the trial
- Ensuring to keep records of the disposition of drug
- Planning and ensuring resources required for the conduct of trial
- Proper maintenance of case histories
- Personally conduct or supervise the study
- Recruitment/Enrolment of the subjects in the study
- Inform subject about the study and obtain informed consent
- Report adverse events to sponsor on time
- Ensure that all subordinate are informed about their duties
- Attend the trial training meeting along with the study team
- Ensure that an IRB will be responsible for reviewing the study and the investigator will promptly inform the IRB of:
  - all changes in the research and not implement until approved by IRB (except if to eliminate an immediate hazard)
  - all unanticipated problems involving risks to subjects.

### Co-investigator

Additional members of the research team, including other physician-investigators, clinical trial nurses, data managers, statisticians, pharmacists, bioethicists, and social workers refer as co-investigator. It is important to document which individuals listed as members of the research team have responsibility for patient care. Each physician-investigator having responsibility for patient care must file a FDA Form 1572 with the sponsor<sup>16</sup>. The co-investigator usually is responsible for the following activities:

- Provide education for the research team and other staff about the general conduct of clinical trials and training for specific trials at the site



- Provide education for the participant and family to help with the decision to participate in the clinical trial and to assist with care during the continuum of the trial
- Check eligibility criteria
- Arrange for study tests
- Collect results of these tests.

### Clinical research nurse

The research nurse participates in the research project as an associate investigator. The Clinical Research Nurse (CRN) is responsible for study protocol compliance including participation in study initiation visits by the sponsor, completion of the IRB submission, amendments, and revisions, recruitment of eligible patients, completion of the informed consent process, coordination of clinic space as necessary for research visits, and scheduling of testing and patient visits in accordance with each specific study schedule, responding to queries from sponsors, and filing of serious adverse event forms. The research nurse may also assume the role as a PI in ancillary protocols involving relevant nursing issues, such as quality of life, patient education, data collection. CRN monitors the participant's use of the investigational agent and interviews the participant about possible adverse event experiences. The CRN might also be responsible for drawing pharmacokinetic samples. Responsibilities of CRN are:

- Ensuring that each patient enrolled on the protocol has met the eligibility criteria
- Ensuring that the protocol consent document has been signed, dated and witnessed before the initiation of any experimental procedure
- Ensuring that all toxicities and adverse events have been documented and reported according to the protocol
- Ensuring that communications are maintained with the patient, the family and all members of the research team
- Presenting nursing-related data at professional meetings
- Publishing nursing-related data in professional journals

### Data manager

The data manager is responsible for all data and the data processing operations. The Clinical Data Manager (CDM) ensures complete, accurate and consistent data for reporting to regulatory bodies. A CDM is involved in the setting up, running and reporting of clinical trials. The CDM processes data using a range of computer applications and database systems to support collection, cleaning and management of patient data. The CDM interacts with client as necessary to establish data review guidelines and data flow procedures. Data manager also

communicate/coordinate with the project manager, statistician, clinical research associate, database manager and clinical sites as needed to ensure accuracy and completeness of the clinical data. This role has changed as electronic systems for clinical trials have evolved. The data manager is often expected to have extensive knowledge of computer systems, remote data capture, and quality assurance. Activities of the data manager include abstracting data from the source documents into the research record, performing quality checks on data, preparing routine reports for patient care, interim monitoring of the trial, and regulatory reporting. Responsibility of data manager are:

- Designing data collection forms
- Collecting data
- Entry of data into specialized forms/data bases
- Observing and reporting trends in data
- Back-up of data
- Security of data
- Publishing relative information in professional journals
- Presentation of relative data management issues at professional meetings

### Statistician

The statistician works closely with the PI early in the writing phase of the protocol to ensure that the trial design is appropriate for the study and that the study is powered to address the study questions. Statistical expertise is essential during the analysis phase of the study, and the statistician is often asked to assist in the written final report of the study.

### Other team member

Depending on the nature of the research, other members could also include in the team such as, bioethicists, pharmacists, social workers, dieticians, radiation specialists, pathologists, and other experts as needed. They should be informed of amendments to the protocol or a change in SOPs that are required for the specific care of a participant enrolled in a clinical trial.

### Study participants

The study participant also called as a study subject, participant, normal volunteer, or a patient. Throughout the clinical trial the safety, dignity and privacy of study participant should be protected. It is well recognized that the person enrolled in a clinical trial is the focus of the research and is offering his or her time and effort in the search for increased knowledge in preventing, treating, or palliating disease. The entire team depends on an educated and dedicated participant to complete the research study since compliance with the study regimen and early notification of potential adverse events is



essential for the participant's safety and the integrity of the trial.

### Informed consent

Informed consent is the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is also a continuing process throughout the study to provide information for participants. To help someone decide whether or not to participate, the doctors and nurses involved in the trial explain the details of the study. If the participant's native language is not English, translation assistance can be provided. Then the research team provides an informed consent document that includes details about the study, such as its purpose, duration, required procedures, and key contacts. Risks and potential benefits are explained in the informed consent document. The participant then decides whether or not to sign the document. Informed consent is not a contract, and the participant may withdraw from the trial at any time. The process of informed consent includes an explanation of the research study to the participant, a discussion of the participant's review of the consent document, and a time for questions and answers. Once the initial component of the process has been completed, the last phase in the process is the request for the participant's signature and date of signing. The consent document is then witnessed by the investigator and additional witnesses as required by the SOPs of the sponsor or the site.

### DISCUSSION

Clinical trials include both interventional and observational types of studies. Interventional studies are those in which the research subjects are assigned by the investigator to a treatment or other intervention, and their outcomes are measured. Observational studies are those in which individuals are observed and their outcomes are measured by the investigators. The clinical trial process depends on the kind of trial being conducted. The clinical trial team includes doctors and nurses as well as social workers and other health care professionals. They check the health of the participant at the beginning of the trial, give specific instructions for participating in the trial, monitor the participant carefully during the trial, and stay in touch after the trial is completed. Some clinical trials involve more tests and doctor visits than the participant would normally have for an illness or condition. For all types of trials, the participant works with a research team. Clinical trial participation is most successful when the protocol is carefully followed and there is frequent contact with the research staff. Data management includes the entire spectrum from data collection and entry to data analysis and reporting. Data management is proactive; it begins while the protocol is being written. It includes a plan for

recruitment of study participants and the management of staff and monetary resources. The good data management tools are a well-written protocol, which includes data collection forms, standard terminologies, with carefully written definitions and a manual of standard operating procedures.

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