

THE CLINICAL TRIAL EXPERIENCE



Clinical Trial Terminology & Definitions

The pharmaceutical industry has its own acronyms (mnemonics) and terminology, especially in relation to clinical trials, clinical research and drug development.

Below is a list of terms with definitions that will help clarify their meanings when used in relation to clinical trials and drug development (**Please Note:** Some definitions have been simplified to aid understanding and are not necessarily a full definition).

Definitions are listed under main headings according to the part of drug development or clinical trials to which they apply.

1. DRUG DEVELOPMENT & CLINICAL TRIAL PROCESSES - GENERAL

Drug Development - The life of a drug from its first idea on paper/in a person's head to the point at which no further development takes place. This could be many years after it was first marketed (many drugs continue some kind of development as new conditions are treated or new dosage forms are developed).

Pre-Clinical - Any work that occurs before a drug or device is used in patients or human volunteers.

Clinical - Any work involving patients i.e., people with an illness, condition or disease.

Clinical Research - Research involving patients. 'Clinical Research' may be substituted for 'Clinical Trial'. The term may also be more loosely applied to any work that takes place at the pharmaceutical company during the clinical phase of drug development e.g., refining stability of a dosage form such as a tablet.

Clinical Trial - A carefully designed and managed study (experiment) which answers specific questions about a drug or device when used in patients.

Phase 0 - A relatively recent designation for exploratory studies which, at a very early stage, determine whether a drug behaves in humans as would be expected from pre-clinical work. Very low ('subtherapeutic') doses of drug may be given to healthy volunteers to gather early data on how the drug's pharmacokinetics and pharmacodynamics. No information on the drug's safety or efficacy can be collected because the dose is too low to cause any therapeutic effect. The use and ethical acceptability of Phase 0 trials has been questioned.

Phase I - The first time a drug is administered to humans. Participants are healthy volunteers. The only exception is when testing toxic drugs, such as for cancer therapy, when the first administration in humans is to patients. Phase I studies take place in dedicated, specialised research units with emergency resuscitation equipment should there be any problems. Focus at Phase I is safety although side-effects may also be noted.



Phase II - The first time a drug is administered to patients. For most drugs, administration to patients follows testing at Phase I in healthy volunteers. However, toxic drugs, such as for cancer therapy, are administered straight into patients at Phase II. Main focus is safety but efficacy is also investigated.

Phase III - Large scale studies confirming safety and efficacy of a drug or device run in hospitals or GP surgeries. There are usually two or more of these pivotal ('key') studies required for registration of a new drug.

Phase IV - These studies, also known as Post Marketing Surveillance Trials, are usually run after registration of a new drug and may be used to show efficacy in new conditions, change a drug's formulation e.g., tablet to capsule, to gain more information in the registered condition e.g., long-term safety, to investigate interactions with other drugs or to investigate its effect certain patient groups e.g., pregnant women.

Drug Registration - The process by which all data generated during a drug's development (pre-clinical & clinical) is submitted for review by Regulatory Authorities in order to gain approval to market the drug. A drug can only be marketed for the conditions, illnesses or infections supported by data from the clinical trial programme.

2. REGULATIONS, RULES & AUTHORITIES

Good Clinical Practice (GCP) - International ethical and scientific quality standard for designing, conducting, monitoring, recording, auditing, analysing and reporting studies. GCP ensures that the data reported is credible and accurate and that subject's/patient's rights and confidentiality are protected.

Committee on the Safety of Medicines (CSM) - The CSM was an independent advisory committee that advised the UK Licensing Authority on the quality, efficacy and safety of medicines for 40 years. It was replaced in 2005 by the Commission on Human Medicines which combines the functions of both the CSM and the Medicines Commission.

Committee on the Safety of Devices (CSD) - Established in 2001, the CSD advises government ministers and complements the work of the MHRA (Devices sector), operating to make medical devices and their use safer and more effective. The CSD, which also advises on the development of device related policies was set up in 2001 and meets two or three times a year.

Medicines and Healthcare products Regulatory Agency (MHRA) - The MHRA is the UK government agency responsible for ensuring that medicines and medical devices work and are acceptably safe. Formed in 2003 by the merger of the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA), it is an executive agency of the Department of Health.

Informed Consent - The process by which a participant (or their legal guardian) voluntarily confirms his or her willingness to take part in a particular trial. Informed consent is usually documented on a written, signed, and dated informed consent form which is completed after all parts of the trial have been clearly explained. Part of the informed consent process is that the patient is made aware that if they decide not to take



part in the trial, their future medical care will not be influenced in any way.

Patient Confidentiality - The process by which any data which can identify and individual patient is kept confidential. Patients are usually identified by a unique study number, allocated when they enter the trial. All medication used by the patient and all documentation related to that patient is identified by the same patient number.

3. STUDY DESIGN & SET-UP

A. Design

Open Label - A clinical trial where investigators and patients know which treatment the patient is receiving.

Blinding - The methods by which the investigator and the participants in a clinical trial are kept unaware of which treatment the patient is receiving. This involves identical labelling and packaging of all study medication, and the use of active and comparator medication (e.g., placebo) which, where possible, looks, tastes and smells identical. If an active comparator medication is used which looks different from the test drug, a double-dummy technique may be used.

Double-Dummy - If a tablet formulation is being tested, each patient receives a combination of tablets for both drugs, such that they receive either active test drug or active comparator only e.g., they may receive 2 tablets: Placebo test drug + Active comparator => The patient receives active comparator overall. NB. This method can be used with other drug formulations and when the test drug and comparator are made as different formulations e.g., liquid for test drug and tablet for comparator.

Single Blind - Usually refers to patients being unaware of the treatment assigned to them, whilst the investigator knows which treatment they have received.

Double Blind - Patients, investigator(s), monitor(s), and data analyst are unaware of the treatment assigned to the patient.

Randomisation - Assigning clinical trial participants to receive active or control treatment by using a randomly generated 'patient assignment to treatment' list. By using this element of chance, the risk of bias through the order of assigning patients to their treatment is minimised.

Parallel Group Design - Study design where each patient receives only one trial drug or treatment e.g., active or placebo treatment.

Crossover Design - Design where each patient receives all trial medications e.g., each patient receives active and placebo treatments. There is period between each treatment where no medication is taken called the 'wash-out period'. The order of drug treatments is carefully determined through randomisation to prevent order of allocation bias.

Bias - Anything which prevents impartial judgment in the way in which a measurement, assessment, procedure, or analysis is carried out or reported.



Baseline - The initial time point in a clinical trial against which all other assessments are compared.

Centre - The location in which a clinical trial takes place e.g., a hospital department or a GCP surgery. For Human Volunteer Studies, the centre is a specially designed and equipped research centre, which usually resembles a hospital ward.

Single Centre - Only one hospital, GP surgery or research centre is used to recruit all patients for a clinical trial. Healthy Volunteer Studies usually only recruit a low number of subjects and are run in a single specialist research centre.

Multicentre - More than one hospital, GP surgery or research centre is used to recruit all patients for a clinical trial. Multicentre trials are used where large numbers of patients are needed (more than can be recruited by one centre/site) or when a high rate of recruitment is needed.

Pharmacokinetics - How the body processes the drug i.e., 'What the body does to the drug'.

Pharmacodynamics - The effects of the drug on the body i.e., 'What the drug does to the body'.

B. Participants

Patient - A person with a condition, illness or infection who requires medical treatment, intervention or supervision.

Subject - A term used to describe any human being that receives medication or treatment as part of a clinical trial, or who receives medication or treatment as part of a human volunteer study. The term subject is widely used in clinical trials to describe patients.

Healthy Volunteer - A healthy individual who volunteers to take part in drug research, usually in response to an advertisement. Phase I research units usually have lists of registered volunteers they can contact for specific studies. Healthy volunteers may be young, or they may be in a specific older age group.

C. Documentation & Data Collection

Standard Operating Procedure (SOPs) - Documents detailing how every aspect of a clinical trial should be written, carried out and reported. Each step in the trial process may have many SOPs to cover in detail each action required e.g., For visits to the study site, there are likely to be separate SOPs detailing initial identification and contact; enrolling and setting-up the site; delivering the study drugs; first monitoring visit; ongoing monitoring visits; final monitoring visit; closing down the study centre and retrieving all study medication etc. The aim of SOPs is to achieve consistency of performance across a study and across different studies.



Protocol - A document describing the objective(s), design, methodology, statistical considerations and organisation of a clinical trial in very fine detail. A study protocol can be more than 100 pages long.

Protocol Amendment - A written description of a change or changes to, or clarification of a protocol. Protocol amendments usually need to be approved by the Ethics Committee before they can be implemented.

Patient Information Leaflet/Patient Information Sheet - A comprehensive information sheet given to all patients so that they can make a fully reasoned decision on whether to take part in a clinical trial. Information on all procedures, assessments, visits, risks, benefits, side-effects, contacts etc are included. This is an integral part of the informed consent process. The term Patient Information Leaflet may be interchanged for Informed Consent Form in some companies.

Informed Consent Form - A document describing the rights of a study participant and providing details about the study, such as its purpose, duration, required procedures, and key contact people. Risks and potential benefits are also explained.

Case Report Forms/Case Record Forms (CRFs) - Forms on which all data required by the protocol for a clinical trial is recorded. CRFs are completed by the investigator and checked by study monitors throughout the study. Any mistakes must be corrected according to strict guidelines as part of GCP. CRFs may be printed, optical, or electronic (eCRF).

Diary Card - A card or booklet in which patients make recordings for the clinical trial in which they are taking part e.g., time of taking their medication.

Remote Data Entry (RDE) - A computerized system for collecting patient data from participants in clinical trials on drugs and/or medical devices.

Source Document - Original documents, data and records e.g., hospital patient records, recorded data from automated instruments, x-rays, etc, that are used in a clinical trial to confirm information entered into the CRFs by the investigator.

Entry/Eligibility Criteria - A list of criteria determining which patients can and cannot enter a clinical trial e.g., Inclusion - participants must be between 55 and 85 years old; Exclusion - participants must not have taken drug X within 3-months of starting the study.

Investigator Brochure - A compilation of the clinical and pre-clinical data on the investigational product(s) which is relevant to its study in human subjects.

D. Drugs & Supplies

New Chemical Entity (NCE) - Also known as New Molecular Entities (NMEs), these are compounds which demonstrate promising activity against a particular biological target thought to be important in disease. Drug development aims to assess safety and efficacy in patients in order that approval to market the drug for a particular condition, infection or



illness can be obtained. Many NCEs never get beyond initial testing for basic activity.

Drug/Agent - A substance used in the diagnosis, treatment, or prevention of a disease or as a component of a medication.

Investigational Product - An active drug or a placebo being tested or used as a reference in a clinical trial. This includes drugs already marketed when used i) in a different formulation, ii) are packaged in a way that is different from the approved form, iii) when used for a new indication which has not yet been approved, or iv) when used to gain further information about an approved use.

Device - A product used for medical purposes in patients, in diagnosis, therapy or surgery. When applied to the body, it has a mainly physical effect (in contrast to pharmaceutical drugs, which exert a biochemical effect). Examples of medical devices include joint replacements, plates for bone splinting and repair, tongue depressors, medical thermometers, blood sugar meters, and X-ray machines.

Dosage Form/Formulation - The state or form in which a drug is delivered to a patient e.g., as a liquid suspension, tablet, capsule, injection etc.

Control - A treatment against which the trial drug is compared. This may be an active comparator or placebo preparation (or both).

Placebo - An inactive pill, liquid, powder, or other formulation or intervention that has no treatment value. In clinical trials, active treatments or test drugs are often compared with a placebo to assess the active treatment's effectiveness.

Comparator Medication - Any medication against which the test drug is being compared. The term 'comparator' usually implies another active drug preparation (placebo being used to describe inactive, control medication).

Blocks/Blocking - The division of all medication to be packed for a clinical trial into smaller units or blocks (typically 4 or 6) for assigning treatment to each patient as they enter the study. For example, in a trial where equal numbers of patients are needed on each of two treatments, a block of say 6 patients would contain 3 patients on Treatment A and 3 patients on Treatment B. Blocking helps to ensure that the ratio of patients on each treatment required by the protocol is achieved during their recruitment into a clinical trial.

Double Tear-Off Labels - Two-part labels attached to study medication, containing identical information on both halves of the label. When the medication is dispensed to the subject during the study, the 'tear-off' portion is removed from the medication and stuck into the patient's CRF as proof that they have received the correct medication.

Blind/Randomisation Codes - The codes generated by the clinical trial supplies department that detail which patient receives what medication. For blinded studies this information is kept hidden unless a patient needs to be withdrawn from a study due to side-effects, when the medication assigned to that patient will be revealed by 'breaking' the blind code i.e., revealing the answer.



4. STUDY SAFETY & APPROVAL

Ethics Committee/Research Ethics Committee - An independent body made up from medical, scientific and non-scientific members ensuring the protection of the rights, safety and well-being of patients/subjects involved in a clinical trial. A trial cannot start without Ethics Committee approval. They also review and approve the methods and materials used to obtain and document informed consent of each trial participant, and provide ongoing review of changes to the trial e.g., protocol amendments.

5. RUNNING & MANAGING THE STUDY

Site/Centre - Location at which patients are recruited into clinical trials and to which patients return for ongoing review and treatment during the trial. A site may be a hospital or a GP's surgery, or in some cases a purpose-built research institute.

A. Study Personnel

Clinical Research Associate (CRA)/Clinical Monitor - Non-medically qualified person within the sponsoring company (company responsible for running and managing the trial) who looks after the trial on a day-to-day basis. Major responsibilities include ensuring smooth running of the trial and integrity of the data provided by the trial site(s).

Medical Monitor - Medically qualified person within the sponsoring company (company responsible for running and managing the trial) with oversight of medically-related issues of a clinical trial, especially relating to safety, classification of adverse events and handling of Serious Adverse Events (SAEs).

Investigator - A medically-qualified person responsible for the conduct of the clinical trial at a trial site and for protecting the integrity, health and welfare of the trial subjects during the trial.

Principal Investigator (PI) - The investigator responsible for a team of investigators at a trial site, or a team of investigators across several trial sites. Under GCP, the Principal Investigator has additional responsibilities.

Research Nurse - A professional person qualified in nursing who assists with research and organises patients for admission and treatment.

B. Processes & Quality

Clinical Monitoring - Oversight and administrative efforts that monitor a participant's health during a clinical trial. The government and other clinical trial funding agencies require data and safety monitoring boards to oversee clinical trials. They want to be certain that safety measures are in place to protect the trial participants.



Audit - A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Quality Assurance (QA) - Systematic approach to ensure that the data are generated, recorded and reported as described by the study protocol and in accordance with Good Clinical Practice (GCP) standards.

Quality Control (QC) - The internal processes and activities undertaken by the organisation responsible for the clinical trial to ensure that all trial related activities have been fulfilled to a sufficiently high standard e.g., data and form checks, monitoring by study staff, routine reports, correction actions, etc.

C. Monitoring Response to Treatment & Safety

Efficacy - How well a drug or device works when it is given to treat a condition, infection or illness.

Safety - The risk of using a drug or device to treat a condition, infection or illness in patients. All drugs affect how the body works and therefore, they will have side-effects: some of these may be beneficial and some may be harmful. The aim is to minimise the harmful effects. Devices may have unwanted side-effects of their own including allergy and toxicity.

Risk:Benefit Ratio - An assessment of the unwanted and desirable effects of a drug or device for determining how suitable it is for use in a given situation. With serious illnesses, such as cancer, the level of acceptable risk is much higher because the outcome is greater e.g., saving life. So patients will be allowed to experience more serious side-effects or adverse effects e.g., vomiting, hair loss, than if the drug was being used to treat a less serious condition e.g., headache, for which remedies with much less serious adverse effects are readily available.

Concomitant Medication - Any other prescription and over-the-counter drugs and supplements that a study participant takes along with their study treatment. Taking certain concomitant medications may be a reason for withdrawing a patient from some studies. Collecting information on concomitant medication may be important for helping to identify previously unseen drug interactions.

Adverse Event (AE) - Any untoward or unfavourable medical occurrence to a patient that occurs whilst they are involved in a clinical trial, whether or not it is thought to relate to trial participation or study drug e.g., tripping and breaking wrist.

Serious Adverse Event (SAE) - A specific category of adverse event defined by regulatory safety authorities as 'Any adverse event that results in death, is life threatening or places the participant at immediate risk of death from the event as it occurred, requires or prolongs hospitalisation, causes persistent or significant disability or incapacity, results in congenital anomalies or birth defects, is another condition which investigators judge to represent significant hazards. Each SAE must be dealt with and reported in a specific and time-constrained manner.



Withdrawal From Study - The act of terminating participation of a patient in a clinical trial before they complete all assessments, visits etc. Withdrawal may be for safety reason or because the patient has not complied with the protocol. Reasons for patient withdrawal before completion are always listed in the protocol.

6. DATA COLLECTION & LOADING INTO DATABASES

Data Management - The processes of handling data collected during a clinical trial, from development of the CRFs through to database locking and transmission of the data to the statistician for final analysis.

Database - A collection of information (data) from a clinical trial, organised so that it can easily be accessed, managed, updated and analysed.

Data Entry - The process of entering information from CRFs into a database. The entry screens are usually set-up to look like the CRF for ease and clarity.

Double data Entry - Data from CRFs is independently entered by two people onto separate parts of the clinical trial database. When all data is entered, the two entry databases are 'merged' and any discrepancies are highlighted and resolved, usually by the study monitor/CRA.

Database Locking - The process of preventing modification of data on a clinical trial database once all of the discrepancies, missing data and other queries have been resolved. Locking the database signals the end of the study conduct phase and the start of the analysis phase.

Unblinding - A procedure in which one or more parties to the trial are made aware of which patients received which treatment(s).

Data Query Form - Coming under a number of different titles, these forms are raised by the data processing group when queries arise concerning completeness or integrity of data. Each form must be answered, signed and dated by either the investigator or Principal Investigator before the information is loaded into the study database.

7. STATISTICS

Statistical Power - In its simplest form, power analysis is a statistical test used to calculate the minimum sample size required to accept the outcome of a statistical test with a particular level of confidence i.e., confirm that the result is unlikely to have happened by chance.

Sample Size - The number of patients needed to show the superiority of one treatment over another/others, or the equivalence of treatments. This calculation is based on the information already known about the drug(s) concerned and the disease, condition etc that it is treating in the clinical trial. Information from previous work is very important in this process.

Error - The difference between a computed, estimated, or measured value and the true value. This may be caused by unpredictable, random, differences



between patients or fluctuations in measurement apparatus used in a trial, or by a combination of the two.

Confidence Intervals (CI) - At its most basic is the range of values in which we are confident that the true value lies. For clinical studies, 95% CI are used, and the most simple interpretation is, 'We can be 95% confident that the true value of the mean for all people with the same condition treated with our drug, lies in this range, based on the results of our study.'

Statistical Significance - The probability that a result occurred by chance alone. In clinical trials, statistical significance depends on the number of participants studied and the observations made, as well as the size of differences observed. Statistical significance may be applied to the difference between treatments, patient characteristics and populations (demographics) etc, but just because a result is statistically significant does not make it clinically relevant.

8. REPORTING & INTERPRETING THE RESULTS

Data Listings - A print-out listing every item of data collected in a clinical trial (usually several hundred pages or more) which is appended to the statistical report.

Statistical Report - Compilation of all data from a clinical trial and the results of its statistical analysis. Results are often tabulated for clarity. The statistical report is the basis on which the final clinical report is written. These two reports are combined into the Integrated Clinical & Statistical Report.

Clinical Report - The final report which brings together and interprets all results from a clinical trial. The clinical significance of the results obtained is interpreted and explained. The clinical report is usually combined with the statistical report to give the Integrated Clinical & Statistical Report.

Integrated Clinical & Statistical Report - The combined statistical and clinical reports which lists and interprets the results of a clinical trial. The clinical significance of the statistical results is also interpreted. All data from the study is listed (this is extensive) and for large studies the report can be more than a thousand pages in total.

Clinical Relevance/Significance - Interpretation by medically qualified personnel of how relevant statistical results are in clinical practice. Statistically significant results may have little clinical significance whilst non-significant results may be very relevant in the clinic. It is the process of converting numbers into reality.





BOOKINGS & FURTHER INFORMATION ON CLINICAL TRIALS TRAINING

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