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A REVIEW ON CLINICAL TRIALS

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ABSTRACT

A clinical trial is a particular type of clinical research that compare on treatment with one another. In clinical trials healthy volunteers, patients or sometimes both are used. Clinical trials are important to find out the action of newly discovered drug molecule on volunteers. Austin Bradford Hill was a pivotal figure in the modern development of clinical trials. It is most important epidemiological method used for testing the hypothesis. In this the pharmacodynamics properties, adverse drug reaction, safety of newly developed drugs are studied. The people who volunteer are randomly assigned to different groups and these subjects are all aware of the drug being given. These subjects do not know which group they are in whether they are in treatment or in placebo group. Clinical trials are studied in 5 phases i.e. phase 0-4. In phase 0 pharmacodynamic and pharmacokinetic properties of drug are studied and for this purpose 10-15 volunteers are used. In phase 1, 20-80 volunteers are used to study safety and adverse drug reaction. In phase 2 large number of volunteers are used i.e.100-300 to study the efficacy of drug against the placebo. In phase 3, 1000-3000 volunteers are used to confirm drug effectiveness, safety, side effect. In phase 4 post marketing study is done to carry out the additional information about the drug i.e. its benefits, treatment risk and its optimal use. The clinical study can be carried out at one location or several locations to know how the drug acts at different locations.

1. OVERVIEW:

1.1 INTRODUCTION:

Clinical trials: Are prospective biomedical or behavioral research studies on human subjects that are designed to answer specific questions about biomedical or behavioral interventions (novel vaccines, drugs, treatments, functional foods, dietary supplements, devices or new ways of using known interventions), generating safety and efficacy data.[1]

What are clinical trials?

A clinical trial is a particular type of clinical research that compares one treatment with another. It may involve patients or healthy people, or both.

Small studies produce less reliable results than large ones, so studies often have to be carried out on a large number of people before the results are considered sufficiently reliable.

Why clinical trials are important?

Doctors and other healthcare professionals and patients need evidence from clinical trials to know which treatments work best. Without this evidence, there is a risk that people could be given treatments that have no advantage, waste NHS resources, and might even be harmful.

Clinical trials help to find out if:

- treatments are safe
- treatments have any side effects
- new treatments are better than available standard treatments

Many NHS treatments have been tested in clinical trials.

The evidence for some treatments is incomplete. The NHS aims to inform patients about research relevant to them and offer more patients the opportunity to take part in clinical trials, if they want to.

Clinical trials can help:

- prevent illnesses by testing a vaccine
- detect or diagnose illnesses by testing a scan or blood test
- treat illnesses by testing a new medicine
- find out how best to provide psychological support
- find out how people can control their symptoms or improve their quality of life by testing how a particular diet affects a condition

Trials follow a set of rules, known as a protocol, to ensure they are well designed and as safe as possible, that they measure the right things in the right way, and that results are

meaningful. A full protocol should be available to anyone who is considering taking part in a trial and wants to see it.

Many clinical trials are designed to show whether new medicines work as expected. These results are sent to the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA then decides whether to allow the company making the medicine to market it for a particular use.

There are four possible outcomes from a clinical trial:

- Positive trial: The clinical trial shows that the new treatment has a large beneficial effect and is superior to standard treatment.
- Non-inferior trial: The clinical trial shows that that the new treatment is equivalent to standard treatment. Also called a non-inferiority trial.
- Inconclusive trial: The clinical trial shows that the new treatment is neither clearly superior nor clearly inferior to standard treatment.
- Negative trial: Clinical trial shows that a new treatment is inferior to standard treatment.

They are conducted only after satisfactory information has been gathered that satisfies health authority/ethics committee approval in the country where approval of the therapy is sought. Small pilot studies, and subsequently conduct progressively larger scale comparative studies. As positive safety and efficacy data are gathered, the number of patients typically increases. Clinical trials can vary in size, and can involve a single research entity in one country or multiple entities in multiple countries.

Depending on product type and development stage, investigators initially enroll volunteers and/or patients into, A full series of trials may cost hundreds of millions of dollars. The burden of paying is usually borne by the sponsor, which may be a governmental organization or a pharmaceutical, biotechnology or medical device company. When the required support exceeds the sponsor's capacity, the trial may be managed by an outsourced partner, such as a contract research organization or an academic clinical trials unit.

1.2 TRIALS OF DEVICES:

Background The medical device manufacturing industry is becoming a major player in health-care delivery. Physicians treat many illnesses and conditions, such as cardiovascular and neurological diseases, with medical devices as often as with medicine. In 2008, for the first time, the FDA received more reports of adverse events from these devices than from pharmaceuticals. Medical device manufacturers can conduct clinical trials more easily in Europe where currently regulatory barriers to clinical testing have less constraints.

Consequently, new innovative medical devices typically come to market in Europe first. Approval for marketing these devices in the US follows in five to ten years, then an additional five to ten years for Japan, which has the longest regulatory pathway.

1.3 TRIALS OF DRUGS:

Clinical trials often involve healthy subjects with no pre-existing medical conditions but sometimes pertain to patients with specific health conditions who seek otherwise unavailable treatments. In early phases, participants are healthy volunteers who receive financial incentives. During dosing periods, study subjects typically remain under supervision for one to 40 nights.

Usually pilot experiments are conducted to gain insights for 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". 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. The benefits must outweigh the risks.[2][3] For example, many drugs to treat cancer 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.[4]

During the trial, investigators recruit patients with the predetermined characteristics, administer the treatment(s) and collect data on the patients' health for a defined time period.

Subjects are volunteers who are not paid for participating. Data include measurements such as vital signs, concentration of the study drug in the blood and/or tissues, changes to symptoms and whether health outcomes. The researchers send the data to the trial sponsor, who then analyzes the pooled data using statistical tests.

Examples of clinical trial goals include assessing the safety and (relative) effectiveness of a medication or device:

- On a specific kind of patient (e.g., patients who have been diagnosed with Alzheimer's disease)
- At a different dose (e.g., 10-mg dose instead of 5-mg dose)
- For a new indication
- Is more effective for the patient's condition than the standard therapy
- Relative to two or more already approved/common interventions for that disease (e.g., device A vs. device B, therapy A vs. therapy B)

While most clinical trials test one alternative to the novel intervention, some expand to three or four. Except for small, single-location trials, the design and objectives are recorded in a document called a clinical trial protocol. The protocol is the trial's 'operating manual' and ensures that all researchers perform the trial in the same way on similar patients and that the data is comparable across all patients.

Because the trial is designed to test hypotheses and rigorously monitor and assess outcomes, they can be seen as an application of the scientific method, specifically theexperimental step.

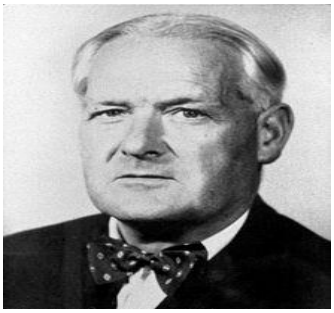
The most common clinical trials evaluate new drugs, medical devices (such as a new catheter), biologics, psychological therapies, or other interventions. Clinical trials may be required before a national regulatory authority. [5]approves marketing of the innovation.

2. HISTORY:

The concepts behind clinical trials are ancient. 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

2.1 DEVELOPMENT:

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 often performed, the use of a control group to provide an accurate comparison for the demonstration of the intervention's efficacy was generally lacking. For instance, Lady Mary Wortley Montagu, who campaigned for the introduction of inoculation (then called variegation) to prevent smallpox, arranged for seven prisoners who had been sentenced to death to undergo variegation 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.[6] The first proper clinical trial was conducted by the physician James Lind.[7] Vitamin C deficiency, would often have terrible effects on the welfare of the crew of long distance voyages. In 1740, the catastrophic result of Anson's circumnavigation attracted much attention in Europe; out of 1900 men, 1400 had died most of them allegedly from having contracted scurvy.[8] John Woodall, an English military surgeon of the British East India Company, had recommended the consumption of citrus fruit (it has an Santiscorbutic effect) from the 17th century, but their use did not become widespread.[9]



2.2 MODERN TRIALS:

Austin Bradford Hill was a pivotal figure in the modern development of clinical trials. The British Medical Research Council officially recognized the importance of clinical trials from the 1930s. 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.

The first randomized curative trial was carried out at the MRC Tuberculosis Research Unit by Sir Geoffrey Marshall (1887–1982). The trial carried out between 1946-1947, aimed to test the efficacy of the chemical streptomycin for curing pulmonary tuberculosis. The trial was both double-blind and placebo-controlled.[10]

International clinical trials day is celebrated on 20 May. [11]

Term	Definition
Subjects	The people who volunteer to take part in the study (sometimes called participants or patients)
Randomized	Subjects are randomly assigned to different groups
Open label	Subjects and researchers are all aware of the drug being given.
Blind	The subjects do not know which group they are in e.g. whether they are in the treatment group or the placebo group.
Double blind	Neither the researchers nor the subjects know to which group the subjects belong until it is revealed at the end of the study.
Placebo	A substance which does not contain the active ingredients of the experimental drug but looks the same (sometimes called a dummy drug).
Add-on	All subjects receive an existing treatment but some then receive the additional experimental drug whilst others do not or are given a placebo
Single centre	The study is carried out at one location
Multi-centre	The study is carried out in several locations (i.e. different towns or even different countries)

3 TYPES:

3.1 DIFFERENT TYPES OF CLINICAL TRIALS:

1) Clinical trial:

Carefully and ethically-designed experiment, in which participating subjects are assigned to the different modes of intervention simultaneously (in the same period of time), at random and are also supervised in a simultaneous way.

Random distribution is the best method for determining that the groups formed are comparable in all the prognostic characteristics except in the intervention they receive.

The clinical trial is the most rigorous epidemiological method for testing hypotheses.

By extension, sometimes any clinical development procedure of a drug is called a clinical trial.

The Law on Medicines and Royal Decree 561/1993 define the clinical trial as: "Any experimental assessment of a substance or medicine, through its administration or application to humans, focusing on one of the following purposes:

1. To find out its pharmacodynamic effects or collect data referring to its absorption, distribution, metabolism and excretion in the human organism;
2. To establish its efficiency for a specific therapeutic, prophylactic or diagnostic indication;
3. To find out the profile of its adverse reactions and establish its safety.

Any study in which the subjects are assigned to one therapeutic intervention group or another at random, or which directly or indirectly conditions the habitual medical prescription process shall always be considered an experimental assessment.

Any study in which an unauthorized substance is used as a pharmaceutical specialty or a pharmaceutical specialty is used in conditions of use which are different from the authorized ones shall always be considered an experimental assessment".

2) Open clinical trial:

Confusing term, used to indicate that a clinical trial does not have any specific methodological characteristic. An open clinical trial is a clinical trial without a control group, as opposed to a controlled clinical trial. It can also be a non-blinded clinical trial, as opposed to a single-blind or double-blind clinical trial.

3) Single-blind clinical trial:

Trial in which the subject, but not the observer, does not know which of the possible treatments he is receiving.

4) Double-blind clinical trial:

Trial in which neither the subject nor the observer know which treatment is being administered.

5) Triple-blind clinical trial:

Clinical trial in which the participating subject, the observer-researcher and the researcher who analyzes the data do not know which treatment is being received.

This is done when the clinical variables examined are soft, that is, they can be interpreted in different ways.

6) Crossover clinical trial:

Clinical trial in which each individual consecutively receives each of the treatments under study.

7) N-of-1 clinical trial:

Trial in which the total population is a single patient and in which the order of administration of the treatments compared is determined in a random way.

8) Explanatory clinical trial:

Said of the trial whose aim is fundamentally to acquire scientific knowledge and biological explanations about efficacy? It is usually done in the earliest phases of the development of a drug, with restricted inclusion criteria, in order to obtain a homogenous sample of participants, representative only of specific sub-groups of population, of a limited size. The main parameters measured are mainly biological ones (for example, deobstruction of coronary arteries in patients who have suffered a myocardial infarction). It is usually done in conditions which are different from those of habitual practice and includes the analysis of patients who complete the trial, as opposed to an intention-to-treat analysis. In explanatory clinical trials it is usually easier to avoid Type-I and Type-II errors, but their power of inference is lower than in pragmatic trials.

9) Unicenter clinical trial:

A trial carried out by a single researcher or research team in one hospital or another type of centre.

10) Multicenter clinical trial:

According to Royal Decree 561/1993, "A trial carried out in two or more centres with the same protocol and a coordinator who is responsible for processing all the data and for analysing the result.

11) Parallel clinical trial:

Clinical trial in which each group of patients receives a single treatment simultaneously.

12) Sequential clinical trial:

Clinical trial in which the observations are assessed as they are produced and the total number of participants is not predetermined, but depends on the accumulated results.

The subjects of the experimental group and the control group are arranged in pairs (one who receives the experimental treatment and the other who receives the reference treatment), are examined and added to the results obtained up to that time.

13) Community trial:

Clinical trial in which the elements allocated randomly are communities or populations, instead of individuals. This is usually carried out when an assessment of the impact of a community intervention is required, for example, fluorination of water (in which populations are randomized) or when it is important to prevent contamination, from one group to another (for example, the periodic administration of Vitamin A supplements to malnourished children, in developing countries).

14) Classification of the types of design:

a) Cross-sectional descriptive studies:

- Prevalence studies.
- Series of cross-sectional cases.
- Evaluation of diagnostic tests
- Concordance studies.
- Case-crossover studies.

b) Longitudinal descriptive studies:

- Incidence studies
- Description of the effects of a non-deliberate intervention
- Natural history description.

c) Observational analytical studies:

- Cause-effect sequence: cohort studies.
- Effect-cause sequence: case-control studies.

d) Experimental analytical studies:

- Controlled trials.
- Uncontrolled trial.

NOTE:

- Experimental clinical trial: study of an osteopathic technique.
- Descriptive or observational analytical trial: study of a diagnostic test.

15) Pilot study:

Initial application, on a small scale, of a study protocol, with the aim of checking whether the design is appropriate, establishing its viability or obtaining information to determine the sample size for the definitive study.

16) Descriptive study:

Part of statistics which summaries the information about the sample. The information collected and summarized in statistics is used to estimate population parameters. Study designed solely for describing the distribution of certain variables, but which is not concerned about the associations between them. It generally has a cross-sectional design.

17) Observational study:

Analytical epidemiological study in which the researcher does not determine the allocation of the subjects to each group, but simply records (observes) what actually happens. It can be a cohort, case-control or cross-sectional study.

a) Observational descriptive study:

This is carried out when little is known about the occurrence, natural history or determinants of a disease. Its objectives include estimating the frequency of a disease or attribute, the temporal trend in a particular population and elaborating or generating more specific etiological hypotheses.

b) Observational analytical study:

An analytical (etiological) study is carried out when enough information is known about the disease before the research, which means that a priori hypotheses already exist and these can be tested in the study. The objectives usually involve identifying risk factors for the disease, estimating the effect of exposure on the disease and therefore deducing possible strategic interventions. Sub-types: cohort studies, and case-controls studies.

18) Experimental study:

In epidemiology, controlled clinical trial or community trial with random distribution. The researcher manipulates the research conditions and randomly distributes the groups. The objective of experimental studies is to estimate the efficacy of a preventive, curative or rehabilitative intervention. The groups which are compared are similar in those characteristics which may have an effect on the response, except for the intervention which is being assessed. The study groups are formed randomly. The use of another active treatment or intervention as a comparative group is to examine the benefit/risk relation of the new treatment in a specific clinical situation.

The control group may be:

- Untreated and its evolution monitored.
- Treated by other means and its evolution compared with another intervention.

19) Cross-sectional studies:

These are studies in which the data of each subject represents essentially a moment of time. This data may correspond to the presence, absence or different degrees of a characteristic or disease. It consists of examining the relationship between different variables in a defined population at a specific moment in time. These designs do not permit the study of an alleged cause-effect relationship. Cross-sectional studies are descriptive by definition. Epidemiological strategy in which observations of numerous factors at the same time are recorded and then a comparison is made between them. The presence or absence of a disease or other variables (or, if they are quantitative, their level) are determined in each subject. The analysis of the results can be made in two senses: by comparing all the variables in the individuals who suffer from the disease being studied, comparing them with those who do not suffer from it, or by comparing prevalence of disease in different subgroups of population.

20) Longitudinal studies:

These are studies in which there is a time lapse between the different variables, so that a time sequence can be established between them. They can be both descriptive and analytical. In analytical studies, it should be taken into account whether the time sequence is from the cause to the outcome (experimental studies and cohort studies), or from the outcome to the cause (case-control studies). Any study not focused on an alleged cause-effect relationship, but whose data is used for purely descriptive purposes is considered descriptive. This type of study is useful for generating etiological hypotheses which should subsequently be contrasted with analytical studies. Any study which evaluates an alleged cause-effect relationship is considered analytical. The alleged causal agent may be a factor which is suspected of being able to lead etiologically to a disease or a treatment to prevent or improve a clinical situation.

21) Feasibility study:

Preliminary study with the objective of determining whether a programme, procedure or study protocol is practicable, as well as finding out data to help in determining the sample size for a definitive study.

22) Crossover study: In clinical trials and in cohort studies, the moving of subjects from the group they were in at the beginning of the observation to another group. In both types of design, the crossover is the cause of the possible differences between the groups compared.

23) Analytical study:

Study designed to examine associations, with the final object usually of identifying or measuring the effects of risk factors or specific interventions on health. Analytical studies can be controlled clinical trials, cohort studies, case-control studies or cross-sectional studies.

24) Prospective study:

Study in which the patients are included from the time the start of the study is decided.

25) Retrospective study:

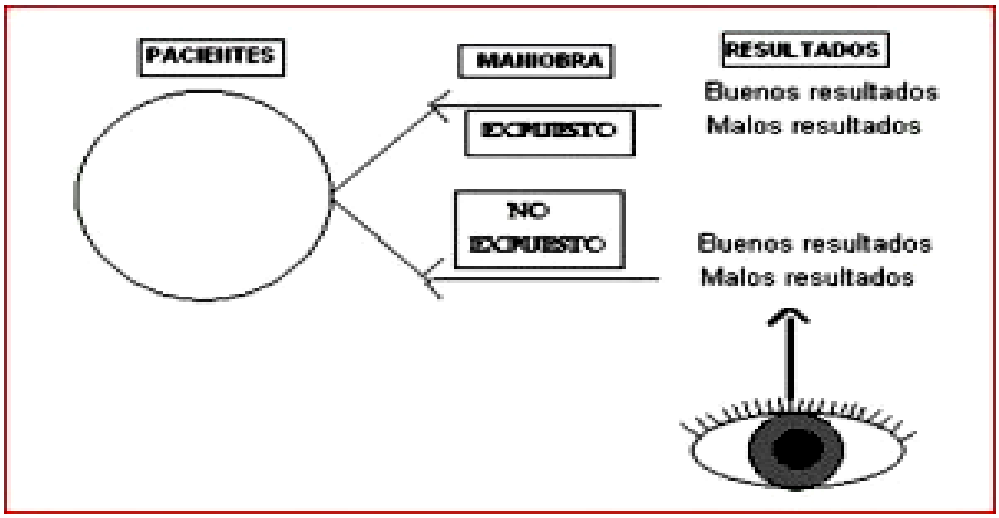
Study in which the data collected refers to events which have occurred.

26) Case-control study:

This type of study identifies people with a disease (or another variable of interest) and compares them with an appropriate control group which does not have the disease. An examination is made, comparing the frequency of exposure to this or other factors between the cases and the controls. It is an analytical observational study which enables the cause-effect relationship to be followed. If the frequency of exposure or the cause is greater in the group of cases with the disease than in the control group, we can say that there is an association between the cause and effect. The measurement of the association which quantifies this association is called the "odds ratio"(OR). In medicine, a case-control study is a cross-sectional type of study which is used to research the etiology of a disease or a given result.

Study in which people with a certain disease or symptom (cases) are compared with others who do not present the disease or symptom under study (controls), with regard to prior exposure to risk factors. This has been incorrectly called Retrospective Study.

In a case-control study, a single disease but various risk factors or exposures are examined.

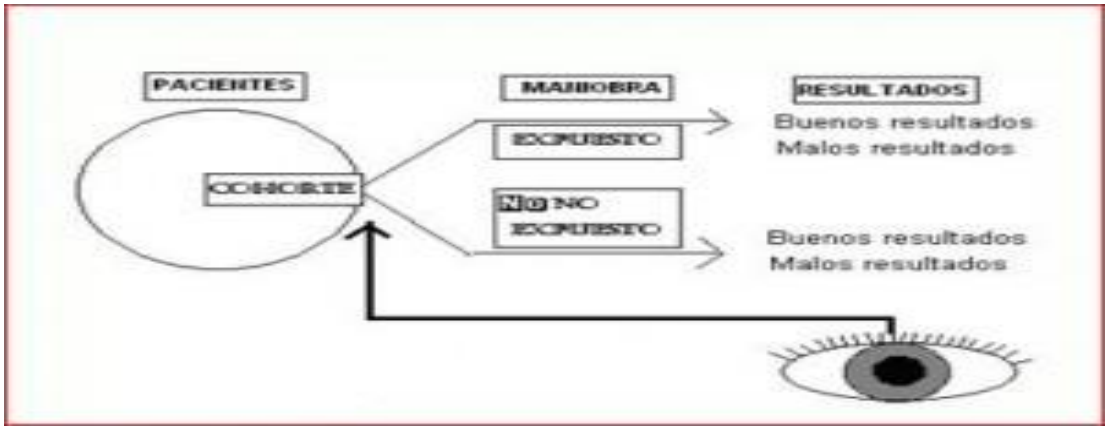


27) Cohort study:

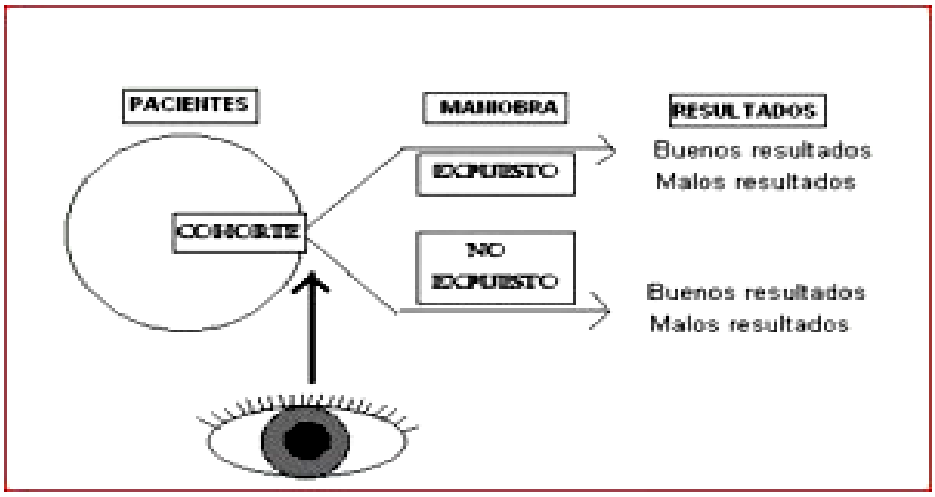
In the Roman militia, a centurial was made up of 60 soldiers.

Two centuries formed a manipulo. The manipulos could be made up of hastate (young, less experienced soldiers, spear throwers or those with swords or light weapons), principes (soldiers with several years of service and several campaigns) or triarii (veterans). At camps and during marches, they formed cohorts, made up of one manipulo of hastatis, one manipulo of principes and one centuria of triarii, that is, a total of 300 soldiers. Epidemiology adopted this term to refer to the idea of a simultaneous advancement, in time, of a group of individuals defined for possessing a common characteristic or group of characteristics. The common characteristic is usually exposure to a factor (environmental, pharmacological, occupational, etc). The term "cohort" is used to designate a group of subjects with a common characteristic or group of characteristics who are monitored over a period of time.

A large number of cases (300 or more) are necessary.



It is an observational, analytical and longitudinal study in which two cohorts differing with regard to the exposure to the factor under study are compared in order to assess a possible cause-effect relationship.



Study in which people subjected to a certain exposure or treatment are compared with people who are not subjected or exposed.

The word “cohort” (from the Latin dehors) means a company of soldiers.

There are prospective cohort studies and retrospective cohort studies; this is why the term is not synonymous with “Prospective study”. [12]

One way of classifying clinical trials is by the way the researchers behave.

- In a clinical observational study, the investigators observe the subjects and measure their outcomes. The researchers do not actively manage the study.
- In an interventional study, the investigators give the research subjects a particular medicine or other intervention. Usually, they compare the treated subjects to subjects who receive no treatment or standard treatment. Then the researchers measure how the subjects' health changes.

Another way of classifying trials is by their purpose:

The U.S. National Institutes of Health (NIH) organizes trials into five different types: [13]

- Prevention trials look for better ways 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.

A third classification is whether the trial design allows changes based on data accumulated during the trial.

- 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 complete.
- Adaptive clinical trials 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.[14] Adaptive trials often employ a Bayesian experimental design to assess the trial's progress. In some cases, trials have become an ongoing process that regularly adds and drops therapies

and patient groups as more information is gained.[15] The aim is to more quickly identify drugs that have a therapeutic effect and to zero in on patient populations for whom the drug is appropriate.[16][17]

Finally, a common way of distinguishing trials is by phase, which in simple terms, relates to how close the drug is to being clinically proven and accepted for use.

3.2 Phases of clinical trial:

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 over many years. If the drug successfully passes through Phases 0, 1, 2, and 3, it will usually be approved by the national regulatory authority for use in the general population. Before pharmaceutical companies start clinical trials on a drug, they will also have conducted extensive preclinical studies.

Phase	Aim	Notes
Phase 0	Pharmacodynamics and pharmacokinetics in humans	Phase 0 trials are the first-in-human trials. Single sub therapeutic doses of the study drug or treatment are given to a small number of subjects (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).[18] For a test drug, the trial documents the absorption, distribution, metabolization, and removal (excretion) of the drug, and the drug's interactions within the body, to confirm that these appear to be as expected.
Phase 1	Screening for safety.	Testing within a small group of people (20–80) to evaluate safety, determine safe dosage ranges, and begin to identify side effects. A drug's side effects could be subtle or long term, or may only happen with a few of people, so phase 1 trials are not expected to identify all side effects.
Phase 2	Establishing the efficacy of the drug, usually against a placebo.	Testing with a larger group of people (100–300) to see if it is effective and to further evaluate its safety. The gradual increase in test group size, allows less common side effects to be progressively sought.
Phase 3	Final confirmation of safety and efficacy.	Testing with large groups of people (1,000–3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely.
Phase 4	Sentry studies during sales.	Post marketing studies delineate additional information, including the treatment's risks, benefits, and optimal use. As such, they are ongoing during the drug's lifetime of active medical use.

4. TRIAL DESIGN:

4.1 ACTIVE COMPARATOR STUDY:

A fundamental distinction in evidence-based practice is between observational studies and randomized controlled trials. 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. In observational studies, the investigators only observe

associations (correlations) between the treatments experienced by participants and their health status. However, under certain conditions, causal effects can be inferred from observational studies.

A randomized controlled trial can provide compelling evidence that the study treatment causes an effect on human health.

Currently, some Phase 2 and most Phase 3 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. This intent is to prevent researchers from treating the two groups differently. A form of double-blind study called a "double-dummy" design allows additional insurance against bias. In this kind of study, all patients are given both placebo and active doses in alternating periods.
- Placebo-controlled: The use of a placebo (fake treatment) allows the researchers to isolate the effect of the study treatment from the placebo effect.

Although the term "clinical trials" is most commonly associated with the large, randomized studies typical of Phase 3, many clinical trials are small. They may be "sponsored" by single researchers or a small group of researchers, and are designed to test simple questions. In the field of rare diseases, sometimes the number of patients is the limiting factor for the size of an **Active comparator study** of note, during the last 10 years or so, it has become a common practice to conduct "active comparator" studies (also known as "active control" trials). In other words, when a treatment is clearly better than doing nothing for the subject (*i.e.* giving them the placebo), the alternate treatment would be a standard-of-care therapy. The study would compare the 'test' treatment to standard-of-care therapy.

A growing trend in the pharmacology field involves the use of third-party contractors to obtain the required comparator compounds. Such third parties provide expertise in the logistics of obtaining, storing, and shipping the comparators. As an advantage to the manufacturer of the comparator compounds, a well-established comparator sourcing agency can alleviate the problem of parallel importing (importing a patented compound for sale in a country outside the patenting agency's sphere of influence).

4.2 MASTER PROTOCOL

In such studies, 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. The first such approach targets squamous cell cancer, which includes varying genetic disruptions from patient to patient. Amgen, AstraZeneca and Pfizer are involved, the first time they have worked together in a late-stage trial. Patients whose genomic profiles do not match any of the trial drugs receive a drug designed to stimulate the immune system to attack cancer.[19]

4.3CLINICAL TRIAL PROTOCOL:

A clinical trial protocol is a document used to define and manage the trial. It is prepared by a panel of experts. All study investigators are expected to strictly observe the protocol.

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.

The protocol contains a precise study plan to assure 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 (often 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.[20] Issued by the international conference on harmonization of technical requirements for registration of pharmaceuticals for human use (ICH).[21] Regulatory authorities in Canada and Australia also follow ICH guidelines. Journals such as Trials, encourage investigators to publish their protocols.

4.4 DESIGN FEATURES:[22]

Statistical power:

The number of subjects has a large impact on the ability to reliably detect and measure effects of the intervention. This is described as its "power". The larger the number of participants, the greater the statistical power and the greater the cost. 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. E.g. Trial of a lipid-lowering drug versus placebo with 100 patients in group might have a power of 0.90 to detect a difference between placebo, trial groups receiving dosage of 10 mg/DL/more, but only 0.70 to detect difference of 5 mg/DL.

4.5 - PLACEBO GROUP:

Merely giving a treatment can have nonspecific effects. These are controlled for by the inclusion of patients who receive only a placebo. 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.

5. ETHICAL ASPECT:

5.1 CLINICAL RESEARCH ETHICS AND CLINICAL TRIALS PUBLICATION

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. The local ethics committee has discretion on how it will supervise nonintervention studies (observational studies or those using already collected data). In the US, this body is called the Institutional Review Board (IRB). 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. In California, the state has prioritized the individuals who can serve as the legally authorized representative. [23]

In some US locations, the local IRB must certify researchers and their staff before they can conduct clinical trials. They must understand the federal patient privacy (HIPAA) law and good clinical practice. The International Conference 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 well being of trial subjects are protected". The notion of informed consent of participating human subjects exists in many countries all over the world, but its precise definition may still vary.

Informed consent is clearly a 'necessary' condition for ethical conduct but does not 'ensure' ethical conduct. The final objective is to serve the community of patients or future patients in a best-possible and most responsible way. 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 (see Odds algorithm), 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.[24]

5.2 CONFLICTS OF INTEREST AND UNFAVORABLE STUDIES:

In response to specific cases in which unfavorable data from pharmaceutical company-sponsored research were not published, 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. [25] The US Congress signed into law a bill which requires phase II and phase III clinical trials to be registered by the sponsor on the the clinical trials website compiled by the National Institutes of Health.[26]

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, e.g., for translational cancer research. 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 no declared industry financial support.[28] Seeding trials are particularly controversial.[29] In the United States, all clinical trials submitted to the FDA as part of a drug approval process are independently assessed by clinical experts within the Food and Drug Administration,[30] including inspections of primary data collection at selected clinical trial sites.[31] 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.[32]

5. SAFETY:

Responsibility for the safety of the 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.

For safety reasons, many clinical trials of drugs are designed to exclude women of childbearing age, pregnant women, and/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.

6.1 SPONSOR:

Throughout the clinical trial, 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. This allows the local investigators to make an informed judgment 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. In larger clinical trials, a sponsor will use the services of a data monitoring committee (DMC, known in the US 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 site 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. This is an area where sponsors can slant their judgment to favor 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. FDA regulations and ICH guidelines both require "the information that is given to the subject or the representative shall be in language understandable to the subject or the representative." If the participant's native language is not English, the sponsor must translate the informed consent into the language of the participant.[33]

6.2 LOCAL SITE INVESTIGATORS:

The ethical principle of primum non nocere guides the trial, and if an investigator believes the study treatment may be harming subjects in the study, the investigator can stop participating

at any time. On the other hand, investigators often have a financial interest in recruiting subjects, and can act unethically to obtain and maintain their participation.

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 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 truly informed consent. They are responsible for reviewing all adverse event reports sent by the sponsor. (These adverse event reports contain the opinion of both the investigator at the site where the adverse event occurred, and the sponsor, regarding the relationship of the adverse event to the study treatments). They 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.

When a local investigator is the sponsor, there may not be formal adverse event reports, but study staff at all locations is 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.

6.3 INSTITUTIONAL REVIEW BOARDS (IRBS):

Approval by an Institutional Review Board (IRB), or ethics board, is necessary before all but the most informal research can 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 scrutinizes the study for both medical safety and protection of the patients involved in the study, before it allows 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.

6.4 REGULATORY AGENCIES :

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). Avoiding an audit is an incentive for investigators to follow study procedures.

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. Critics have argued that clinical trials performed outside the U.S. allow companies to avoid many of the FDA's regulations, since the FDA audits these trials less frequently than U.S. studies. For drug applications approved by the FDA in 2008, 0.7 percent of foreign clinical study sites were audited by the FDA compared to 1.9 percent domestically. Other criticisms of foreign clinical studies, especially in developing countries, relate to the rights and welfare of study participants, integrity of study data, and relevance of data to the U.S. population.[34][35]

Different countries have different regulatory requirements and enforcement abilities. 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", says Jacob Sijtsma of the Netherlands-based WEMOS, an advocacy health organization tracking clinical trials in developing countries.[36]

Beginning in 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),[37] 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."[38]

7. ECONOMICS:

7.1SPONSOR:

The cost of a study depends on many factors, especially the number of sites conducting the study, the number of patients required, and whether the study treatment is already approved for medical use. Clinical trials follow a standardized process.

The costs to a pharmaceutical company of administering a Phase 3 or 4 clinical trials may include, among others:

- manufacturing the drug(s)/device(s) tested
- staff salaries for the designers and administrators of the trial
- payments to the contract research organization, the site management organization (if used) and any outside consultants
- payments to local researchers (and their staffs) for their time and effort in recruiting patients and collecting data for the sponsor
- study materials and shipping
- communication with the local researchers, including on-site monitoring by the CRO before and (in some cases) multiple times during the study
- one or more investigator training meetings
- costs incurred by the local researchers, such as pharmacy fees, IRB fees and postage
- any payments to patients enrolled in the trial (all payments are strictly overseen by the IRBs to ensure the patients do not feel coerced to take part in the trial by overly attractive payments)

These costs are incurred over several years.

In the US, sponsors may receive a 50% tax credit for clinical trials of drugs being developed for the treatment of rare (orphan) diseases.[39]

National health agencies, such as the US National Institutes of Health, offer grants to investigators who design clinical trials that attempt to answer research questions of interest to the agency. In these cases, the investigator who writes the grant and administers the study acts as the sponsor, and coordinates data collection from any other sites. These other sites may or may not be paid for participating in the study, depending on the amount of the grant and the amount of effort expected from them.

Clinical trials are traditionally expensive and difficult to undertake. Using internet resources can, in some cases, reduce the economic burden.[40] New technologies enable sponsors and CRO's to reduce trial costs by executing online feasibility assessments and better collaborate with research centers such as Vis Research Institute.

7.2 INVESTIGATORS:

Many clinical trials do not involve any money. However, when the sponsor is a private company or a national health agency, investigators are almost always paid to participate. These amounts can be small, just covering a partial salary for research assistants and the cost

of any supplies (usually the case with national health agency studies), or be substantial and include 'overhead' that allows the investigator to pay the research staff during times between clinical trials.

7.3 SUBJECTS:

Participants in Phase 1 drug trials do not gain any direct benefit from taking part. They are generally paid an inconvenience allowance because they give up their time (sometimes away from their homes); the amounts paid are regulated and are not related to the level of risk involved. In most other trials, subjects are not paid to ensure their motivation for participating is the hope of getting better or contributing to medical knowledge, without their judgment being skewed by financial considerations. However, they are often given small payments for study-related expenses such as travel or as compensation for their time in providing follow-up information about their health after they are discharged from medical care.

7.4 PARTICIPATION AS LABOR:

It has been suggested that clinical trial participants be considered to be performing 'experimental' or 'clinical labor'. Re-classifying clinical trials as labor is supported by the fact that information gained from clinical trials contributes to biomedical knowledge,[41] and thus increases the profits of pharmaceutical companies. The labor performed by those participants in clinical trials includes the provision of tissue samples and information, the performance of other tasks, such as adhering to a special diet, or (in the case of Phase I trials particularly) exposing themselves to risk.[42] The participants in exchange are offered potential access to medical treatment. For some, this may be a treatment with the potential to succeed where other treatments have failed. For other individuals, particularly those situated in countries such as China or India, they may be given access to healthcare which they otherwise would be unable to afford, for the duration of the trial.[43][44][45] Thus, the exchange which exists may serve to classify clinical trials as a form of labor.

8. PARTICIPATING IN A CLINICAL TRIAL:

Phase 0 and Phase 1 drug trials seek healthy volunteers. Most other clinical trials seek patients who have a specific disease or medical condition. The diversity observed in society, by consensus, should be reflected in clinical trials through the appropriate inclusion of ethnic minority populations.[46] Patient recruitment plays a significant role in the activities and responsibilities of sites conducting clinical trials.

8.1 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.

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.[47] Other disease-specific services exist for volunteers to find trials related to their condition.[48] Volunteers may search directly on ClinicalTrials.gov to locate trials using a registry run by the U.S. National Institutes of Health and National Library of Medicine.

However, many clinical trials will not accept participants who contact them directly to volunteer, as it is believed this may bias the characteristics of the population being studied. Such trials typically recruit via networks of medical professionals who ask their individual patients to consider enrollment.

8.2 STEPS FOR VOLUNTEERS:

Before participating in a clinical trial, interested volunteers should speak with their doctors, family members, and others who have participated in trials in the past. After locating a trial, volunteers will often have the opportunity to speak or e-mail the clinical trial coordinator for more information and to answer any questions. After receiving consent from their doctors, volunteers then arrange an appointment for a screening visit with the trial coordinator. [49]

All volunteers being considered for a trial are required to undertake a medical screening. Requirements differ for different trials, but typically volunteers will have the following tests in a medical laboratory:[50]

- Measurement of the electrical activity of the heart (ECG)
- Measurement of blood pressure, heart rate and temperature
- Blood sampling
- Urine sampling
- Weight and height measurement
- Drugs abuse testing
- Pregnancy testing (females only)

8.3 Research:

In 2012, Z. Janet Yang, Katherine A. McComas, Geri K. Gay, John P. Leonard, Andrew J. Dannenberg, and Hildy Dillon conducted research on the attitudes towards clinical trial treatment and the decision making of signing up for such trials by cancer patients and the general population. They used the risk information seeking and processing (RISP) model to

analyze the social implications that affect attitudes and decision making pertaining to clinical trials. People who hold a higher stake or interest in clinical trial treatment showed a greater likelihood of seeking information about clinical trials. Those with networks that stress the importance of learning about clinical trials are also more likely to seek and process information more deeply. People with more knowledge about clinical trials tend to have to a greater likelihood of signing up. In the study, 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]

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