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Key concepts of clinical trials and their regulations: A review

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Abstract

A clinical trial is a research study in human volunteers to answer specific health questions. Carefully conducted clinical trials are fastest and safest way to find treatment that work in people and way to improve health. Investigational trials determine whether experimental treatment or new ways of using known therapies are safe and effective under controlled environment. Observational trials address health issues in large groups of people or population in natural settings. Clinical trials aim to measure therapeutic effectiveness and constitute an important and highly specialized form of biological assay. In phase I pharmacokinetics, safety, gross effects are studied on human volunteers, by clinical pharmacologists. If the drug passes the test, it enters phase II testings, where pharmacokinetics, safety, therapeutic efficiency are studied on selected patients by clinical pharmacologist, if passes hundreds of selected patients are now studied, primarily for safety and therapeutic effectiveness by clinical investigators in phase III. If this is passed the drug is now approved and marketed. Even after marketing, physicians from various hospitals and clinics send their opinion about the drug, regarding ADR, efficacy in phase IV.

Keywords: Clinical trials, preclinical studies, clinical studies, NDA

1. Introduction

Clinical trials are prospective biomedical or behavioural research studies on human subjects that are designed to answer specific questions about biomedical or behavioural interventions (novel vaccines, drugs, treatments, devices or new ways of using known interventions), generating safety and efficacy data^[1, 2]. 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. Depending on product type and development stage, investigators initially enroll volunteers and/or patients into 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. 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^[3].

2. Clinical study design

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^[4].

- 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 a clinical trial.

Active comparator studies

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 [5].

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.

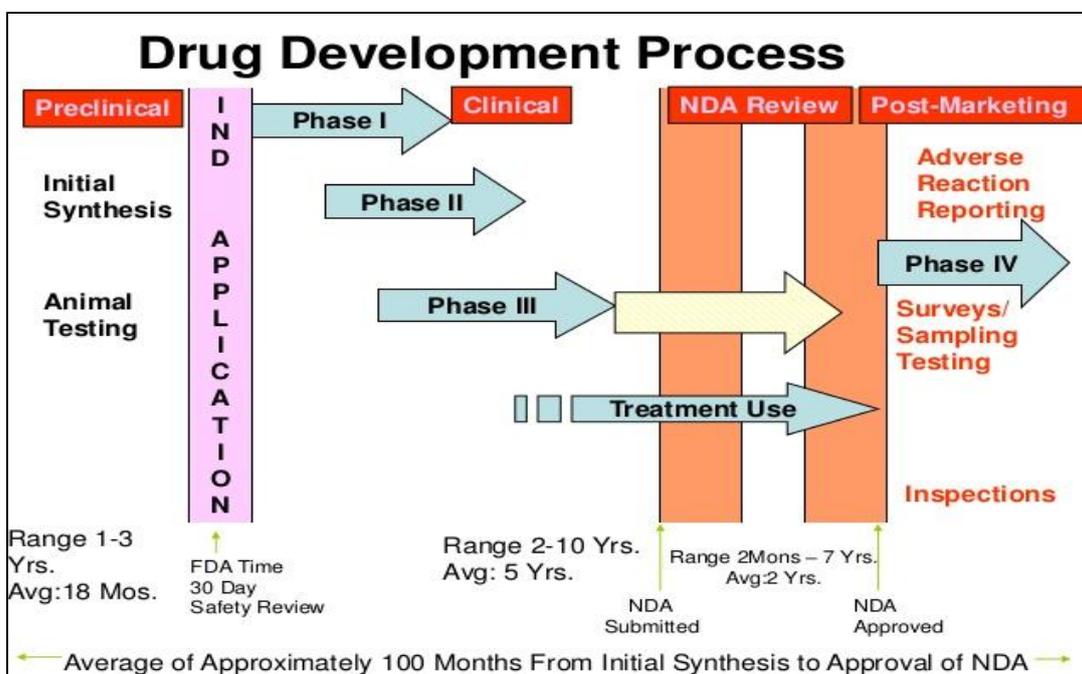


Fig 1: Drug Development Process

3. Clinical trial protocol [6,7]

A clinical trial protocol is a document used 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). Regulatory authorities in Canada and Australia also follow ICH guidelines. Journals such as *Trials*, encourage investigators to publish their protocols.

Informed consent

Clinical trials recruit study subjects to sign a document representing their "informed consent". [22] The document includes details such as its purpose, duration, required procedures, risks, potential benefits and key contacts. The participant then decides whether to sign the document. The document is not a contract, as the participant can withdraw at any time without penalty. Informed consent is a legal process in which a recruit is instructed about key facts before deciding

whether to participate. Researchers explain the details of the study in terms the subject can understand. The information is presented in the subject's native language. Generally, children cannot autonomously provide informed consent, but depending on their age and other factors, may be required to provide informed assent [8].

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. For example, a trial of a lipid-lowering drug versus placebo with 100 patients in each group might have a power of 0.90 to detect a difference between placebo and trial groups receiving dosage of 10 mg/dL or more, but only 0.70 to detect a difference of 5 mg/dL.

Placebo-controlled studies

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 doubled-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.

4. Phases of clinical research [8-10]

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.

- Phase 0: Pharmacodynamics and Pharmacokinetics
- Phase 1: Screening for safety
- Phase 2: Establishing the efficacy of the drug, usually against a placebo
- Phase 3: Final confirmation of safety and efficacy
- Phase 4: Sentry studies during sales

Each phase has a different purpose and helps scientists answer a different question:

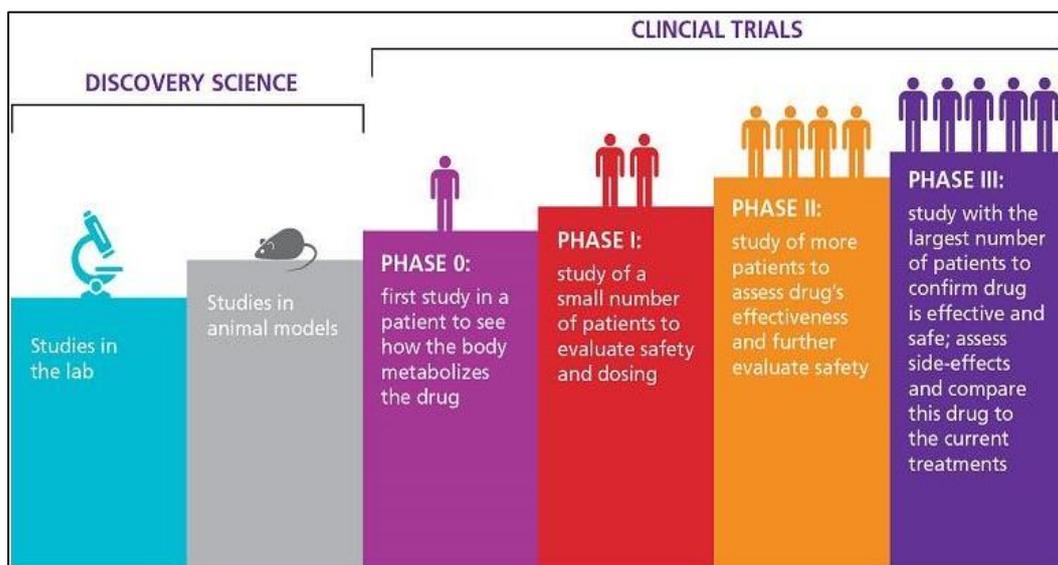


Fig 2: Phases of Clinical Trails

Phase 0 trials

Phase 0 trials are the first-in-human trials. Single sub therapeutic doses of the study drug 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), It is Also called as Micro Dosing Study.

Phase 1 trials

In Phase 1 trials, researchers test an experimental drug or treatment in a small group of people (20–80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

Phase 2 trials

In Phase 2 trials, the experimental treatment is given to a larger group of people (100–300) to see if it is effective and to further evaluate its safety.

Phase 3 trials

In Phase 3 trials, the treatment is given to 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 trials

In Phase 4 trials, post marketing studies delineate additional information, including the treatment's risks, benefits, and optimal use.

Before pharmaceutical companies start clinical trials on a drug, they conduct extensive preclinical studies.

5. Clinical research ethics and Clinical trials publication [11-13]

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 non interventional 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.

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 Harmonisation 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 (paediatrics).

Commercial ties and unfavourable studies ^[14,15]

Due to repeated accusations and findings that some clinical trials conducted or funded by pharmaceutical companies may report only positive results for the preferred medication, the industry has been looked at much more closely by independent groups and government agencies.

In response to specific cases in which unfavorable data from pharmaceutical company-sponsored research was not published, the Pharmaceutical Research and Manufacturers of America have published new guidelines urging companies to report all findings and limit the financial involvement in drug companies of researchers. US congress signed into law a bill which requires phase II and phase III clinical trials to be registered by the sponsor on the clinical trials website run by the NIH.

Drug researchers not directly employed by pharmaceutical companies often look to companies for grants, and companies often look to researchers for studies that will make their products look favorable. Sponsored researchers are rewarded by drug companies, for example with support for their conference/symposium costs. Lecture scripts and even journal articles presented by academic researchers may actually be 'ghost-written' by pharmaceutical companies. Some researchers who have tried to reveal ethical issues with clinical trials or who tried to publish papers that show harmful effects of new drugs or cheaper alternatives have been threatened by drug companies with lawsuits.

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.

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 favour 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.

Local site investigators

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 staffs at all locations are responsible for informing the coordinating investigator of anything unexpected. The local investigator is responsible for being truthful to the local IRB in all communications relating to the study.

Institutional review boards (IRBs)

Approval by an Institutional Review Board (IRB), or 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.

Regulatory agencies

If a clinical trial concerns a new regulated drug or medical device (or an existing drug for a new purpose), the appropriate regulatory agency for each country where the sponsor wishes to sell the drug or device is supposed to review all study data before allowing the drug/device to proceed to the next phase, or to be marketed. However, if the sponsor withholds negative data, or misrepresents data it has acquired from clinical trials, the regulatory agency may make the wrong decision. However, if leaders of the regulatory agency are friendly to industry, they may pressure staff scientists to make decisions favorable to industry, disregard their findings, or make it otherwise difficult for them to do their job. 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.

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 Dr. Jacob Sijtsma of the Netherlands-based WEMOS, an advocacy health organisation tracking clinical trials in developing countries. 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 Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) 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.

Economics

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 trial 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)

In the US, sponsors may receive a 50% tax credit for certain clinical trials. 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 ^[43]. 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.

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.

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.

Participation as labour

It has been suggested that clinical trial participants be considered to be performing 'experimental' or 'clinical labour'. Re-classifying clinical trials as labour is supported by the fact that information gained from clinical trials contributes to biomedical knowledge ^[44], and thus increases the profits of pharmaceutical companies. The labour 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. 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. Thus, the exchange which exists may serve to classify clinical trials as a form of labour. 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. Patient recruitment plays a significant role in the activities and responsibilities of sites conducting clinical trials.

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. Other disease-specific services exist for volunteers to find trials related to their condition. 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 enrolment.

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 ^[52].

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:

- 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)

6. Conclusion

A clinical trial for any new drug follows under the guidelines of ICH and GCP, clinical trial are conducted in human volunteers for confirmation of useful properties of new drug. After preclinical development, investigational new drug passes through clinical phases I, II, III and IV. These phases provide in detail explanation of pharmacokinetic, pharmacodynamics profile and side effect which may be harmful or beneficial, adverse effect and post marketing surveillance.

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