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A BRIEF REVIEW ON CLINICAL TRIALS

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ABSTRACT

A fundamental distinction in evidence-based medicine 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 between the treatments experienced by participants and their health status or diseases.

Keywords: Clinical Trials, Drugs, Diagnostics, Devices, Therapy Protocols.

INTRODUCTION

Clinical trials are a set of procedures in medical research and drug development that are conducted to allow safety (or more specifically, information about adverse drug reactions and adverse effects of other treatments) and efficacy data to be collected for health interventions (e.g., drugs, diagnostics, devices, therapy protocols). These trials can take place only after satisfactory information has been gathered on the quality of the non-clinical safety, and Health Authority/Ethics Committee approval is granted in the country where the trial is taking place.

Depending on the type of product and the stage of its development, investigators enroll healthy volunteers and/or patients into small pilot studies initially, followed by larger scale studies in patients that often compare the new product with the currently prescribed treatment. As positive safety and efficacy data are gathered, the number of patients is typically increased. Clinical trials can vary in size from a single center in one country to multicenter trials in multiple countries.

Due to the sizable cost a full series of clinical trials may incur, the burden of paying for all the necessary people and services is usually borne by the sponsor who may be a governmental organization, a pharmaceutical, or biotechnology company. Since the diversity of roles may exceed resources of the sponsor, often a clinical trial is otherwise unavailable treatments. In early phases, participants are healthy volunteers who receive financial incentives for their inconvenience. During dosing periods, study subjects typically remain on site at the unit for durations of anything from 1 to 30 nights, occasionally longer, although this is not always required.

In planning a clinical trial, the sponsor or investigator first identifies the medication or device to be tested. Usually, one or more pilot experiments are conducted to gain insights for design of the clinical trial to follow. In medical jargon, effectiveness is how well a treatment works in practice and efficacy is how well it works in a clinical trial. In the U.S., the elderly comprise only 14% of the population but they consume over one-third of drugs. Despite this, they are often excluded from trials because their more frequent health issues and drug use produce unreliable data. Women, children, and people with unrelated medical conditions are also frequently excluded.

In coordination with a panel of expert investigators (usually physicians well known for their publications and clinical experience), the sponsor decides what to compare the new agent with (one or more existing treatments or a placebo), and what kind of patients might benefit from the medication or device.

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During the clinical trial, the investigators: recruit patients with the predetermined characteristics, administer the treatment(s), and collect data on the patients' health for a defined time period. These patients are volunteers and they are not paid for participating in clinical trials. These data include measurements like vital signs, concentration of the study drug in the blood, and whether the patient's health improves or not. The researchers send the data to the trial sponsor who then analyzes the pooled data using statistical tests [1].

Some examples of what a clinical trial may be designed to do:

- Assess the safety and effectiveness of a new medication or device on a specific kind of patient (e.g., patients who have been diagnosed with Alzheimer's disease)
- Assess the safety and effectiveness of a different dose of a medication than is commonly used (e.g., 10 mg dose instead of 5 mg dose)
- Assess the safety and effectiveness of an already marketed medication or device for a new indication, i.e. a disease for which the drug is not specifically approved
- Assess whether the new medication or device is more effective for the patient's condition than the already used, standard medication or device ("the gold standard" or "standard therapy")
- Compare the effectiveness in patients with a specific disease of two or more already approved or common interventions for that disease (e.g., Device A vs. Device B, Therapy A vs. Therapy B)

Note that while most clinical trials compare two medications or devices, some trials compare three or four medications, doses of medications, or devices against each other.

Except for very small trials limited to a single location, the clinical trial design and objectives are written into a document called a clinical trial protocol. The protocol is the 'operating manual' for the clinical trial and ensures that researchers in different locations all perform the trial in the same way on patients with the same characteristics. (This uniformity is designed to allow the data to be pooled.) A protocol is always used in multicenter trials.

Because the clinical trial is designed to test hypotheses and rigorously monitor and assess what happens, clinical trials can be seen as the application of the scientific method, and specifically the experimental step, to understanding human or animal biology.

The most commonly performed clinical trials evaluate new drugs, medical devices (like a new catheter), biologics, psychological therapies, or other interventions. Clinical trials may be required before the national regulatory authority approves marketing of the drug or device, or a new dose of the drug, for use on patients.

History

The concepts behind clinical trials, however, 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 and philosopher, Avicenna, gave such inquiries a more formal structure. In *The Canon of Medicine* in 1025 AD, he laid down rules for the experimental use and testing of drugs and wrote a precise guide for practical experimentation in the process of discovering and proving the effectiveness of medical drugs and substances. He laid out the following rules and principles for testing the effectiveness of new drugs and medications:

1. The drug must be free from any extraneous accidental quality.
2. It must be used on a simple, not a composite, disease.
3. The drug must be tested with two contrary types of diseases, because sometimes a drug cures one disease by its essential qualities and another by its accidental ones.
4. The quality of the drug must correspond to the strength of the disease. For example, there are some drugs whose heat is less than the coldness of certain diseases, so that they would have no effect on them.
5. The time of action must be observed, so that essence and accident are not confused.
6. The effect of the drug must be seen to occur constantly or in many cases, for if this did not happen, it was an accidental effect.
7. The experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man.

One of the most famous clinical trials was James Lind's demonstration in 1747 that citrus fruits cure scurvy. He compared the effects of various different acidic substances, ranging from vinegar to cider, on groups of afflicted sailors, and found that the group who were given oranges and lemons had largely recovered from scurvy after 6 days.

Frederick Akbar Mahomed, who worked at Guy's Hospital in London, made substantial contributions to the process of clinical trials during his detailed clinical studies, where "he separated chronic nephritis with secondary hypertension from what we now term essential hypertension." He also founded "the Collective Investigation Record for the British Medical Association; this organization collected data from physicians practicing outside the hospital setting and was the precursor of modern collaborative clinical trials and t123 [2].

Types

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

- In an observational study, the investigators observe the subjects and measure their outcomes. The researchers do not actively manage the study. An example is the Nurses' Health 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 (5) different types:

- *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*: 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*: explore ways to improve comfort and the quality of life for individuals with a chronic illness (a.k.a. Supportive Care trials).
- *Compassionate use trials* or *expanded access*: provide partially tested, unapproved therapeutics prior to a small number of patients that have no other realistic options. Usually, this involves a disease for which no effective therapy exists, or a patient that has already attempted and failed all other standard treatments and whose health is so poor that he does not qualify for participation in randomized clinical trials. Usually, case by case approval must be granted by both the FDA and the pharmaceutical company for such exceptions [3].

Clinical study design

A fundamental distinction in evidence-based medicine 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 or diseases.

A randomized controlled trial is the study design that can provide the most compelling evidence that the study treatment causes the expected effect on human health. Currently, some Phase II and most Phase III 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 is being given to any given subject. This 'blinding' is to prevent biases, since if a physician knew which patient was getting the study treatment and which patient was getting the placebo, he/she might be tempted to give the (presumably helpful) study drug to a patient who could more easily benefit from it. In addition, a physician might give extra care to only the patients who receive the placebos to compensate for their ineffectiveness. A form of double-blind study called a "double-dummy" design allows additional insurance against bias or placebo effect. In this kind of study, all patients are given both placebo and active doses in alternating periods of time during the study.
- Placebo-controlled: The use of a placebo (fake treatment) allows the researchers to isolate the effect of the study treatment.

Although the term "clinical trials" is most commonly associated with the large, randomized studies typical of Phase III, many clinical trials are small. They may be "sponsored" by single physicians or a small group of physicians, and are designed to test simple questions. In the field of rare diseases sometimes the number of patients might be the limiting factor for a clinical trial. Other clinical trials require large numbers of participants (who may be followed over long periods of time), and the trial sponsor is a private company, a government health agency, or an academic research body such as a university [4].

Active comparator studies

Of note, during the last ten 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 exists that 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).

Clinical trial protocol

A clinical trial protocol is a document used to gain confirmation of the trial design by a panel of experts and adherence by all study investigators, even if conducted in various countries.

The protocol describes the scientific rationale, objective(s), design, methodology, statistical considerations, and organization of the planned trial. Details of the trial are also provided in other documents referenced in the protocol such as an Investigator's Brochure.

The protocol contains a precise study plan for executing the clinical trial, not only to assure safety and health of the trial subjects, but also to provide an exact template for trial conduct by investigators at multiple locations (in a "multicenter" trial) to perform the study in exactly the same way. This harmonization allows data to be combined collectively as though all investigators (referred to as "sites") were working closely together. The protocol also gives the study administrators (often a contract research organization or CRO) as well as the site team of physicians, nurses and clinic administrators a common reference document for site responsibilities during the trial.

The format and content of clinical trial protocols sponsored by pharmaceutical, biotechnology or medical device companies in the United States, European Union, or Japan has been standardized to follow Good Clinical Practice guidance[15] 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. Some journals, e.g. *Trials*, encourage trialists to publish their protocols in the journal [5].

DESIGN FEATURES

Informed consent

An essential component of initiating a clinical trial is to recruit study subjects following procedures using a signed document called "informed consent". Generally, children participating in clinical trial cannot autonomously provide informed consent, but depending on their age and other factors may be required to provide informed assent.

Informed consent is a legally-defined process of a person being told about key facts involved in a clinical trial before deciding whether or not to participate. To fully describe participation to a candidate subject, the doctors and nurses involved in the trial explain the details of the study using terms the person will understand. Foreign language translation is provided if the participant's native language is not the same as the study protocol.

The research team provides an informed consent document that includes trial details, such as its purpose, duration, required procedures, risks, potential benefits and key contacts. The participant then decides whether or not to sign the document in agreement. Informed consent is not an immutable contract, as the participant can withdraw at any time without penalty.

Statistical power

The number of patients enrolled in a study has a large bearing on the ability of the study to reliably detect the size of the effect of the study intervention. This is described as the "power" of the trial. The larger the sample size or number of participants in the trial, the greater the statistical power.

However, in designing a clinical trial, this consideration must be balanced with the fact that more patients make for a more expensive trial. The power of a trial is not a single, unique value; it estimates the ability of a trial to detect a difference of a particular size (or larger) between the treated (tested drug/device) and control (placebo or standard treatment) groups. By 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 patients receiving study drug and patients receiving placebo of 10 mg/dL or more, but only have a power of 0.70 to detect a difference of 5 mg/dL [6].

Placebo groups

Merely giving a treatment can have nonspecific effects, and these are controlled for by the inclusion of a placebo group. Subjects in the treatment and placebo groups are assigned randomly and blinded as to which group they belong. Since researchers can behave differently to subjects given treatments or placebos, trials are also doubled-blinded so that the researchers do not know to which group a subject is assigned.

Assigning a person 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.

Phases

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 I, II, and III, it will usually be approved by the national regulatory authority for use in the general population.

- Phase I: Screening for safety
- Phase II: Establishing the testing protocol

- Phase III: Final testing
- Phase IV: 'Post-approval' studies

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

Length

Clinical trials are only a small part of the research that goes into developing a new treatment. Potential drugs, for example, first have to be discovered, purified, characterized, and tested in labs (in cell and animal studies) before ever undergoing clinical trials. In all, about 1,000 potential drugs are tested before just one reaches the point of being tested in a clinical trial.[] For example, a new cancer drug has, on average, 6 years of research behind it before it even makes it to clinical trials. But the major holdup in making new cancer drugs available is the time it takes to complete clinical trials themselves. On average, about 8 years pass from the time a cancer drug enters clinical trials until it receives approval from regulatory agencies for sale to the public. Drugs for other diseases have similar timelines [8].

Some reasons a clinical trial might last several years:

- For chronic conditions like cancer, it takes months, if not years, to see if a cancer treatment has an effect on a patient.
- For drugs that are not expected to have a strong effect (meaning a large number of patients must be recruited to observe *any* effect), recruiting enough patients to test the drug's effectiveness (i.e., getting statistical power) can take several years.
- Only certain people who have the target disease condition are eligible to take part in each clinical trial. Researchers who treat these particular patients must participate in the trial. Then they must identify the desirable patients and obtain consent from them or their families to take part in the trial.

The biggest barrier to completing studies is the shortage of people who take part. All drug and many device trials target a subset of the population, meaning not everyone can participate. Some drug trials require patients to have unusual combinations of disease characteristics. It is a challenge to find the appropriate patients and obtain their consent, especially when they may receive no direct benefit (because they are not paid, the study drug is not yet proven to work, or the patient may receive a placebo). In the case of cancer patients, fewer than 5% of adults with cancer will participate in drug trials. According to the Pharmaceutical Research and Manufacturers of America (PhRMA), about 400 cancer medicines were being tested in clinical trials in 2005. Not all of these will prove to be useful, but those that are may be delayed in getting approved because the number of participants is so low.

For clinical trials involving a seasonal indication (such as airborne allergies, Seasonal Affective Disorder, influenza, and others), the study can only be done during a limited part of the year (such as Spring for pollen allergies), when the drug can be tested. This can be an additional complication on the length of the study, yet proper planning and the use of trial sites in the southern as well as northern hemispheres allows for year-round trials can reduce the length of the studies.

Clinical trials that do not involve a new drug usually have a much shorter duration. (Exceptions are epidemiological studies like the Nurses' Health Study [9].

Administration

Clinical trials designed by a local investigator and (in the U.S.) federally funded clinical trials are almost always administered by the researcher who designed the study and applied for the grant. Small-scale device studies may be administered by the sponsoring company. Clinical trials of new drugs are usually administered by a contract research organization (CRO) hired by the sponsoring company. The sponsor provides the drug and medical oversight. A CRO is a company that is contracted to perform all the administrative work on a clinical trial. For Phase II, III and IV the CRO recruits participating researchers, trains them, provides them with supplies, coordinates study administration and data collection, sets up meetings, monitors the sites for compliance with the clinical protocol, and ensures that the sponsor receives data from every site. Specialist site management organizations can also be hired to coordinate with the CRO to ensure rapid IRB/IEC approval and faster site initiation and patient recruitment. Phase I clinical trials of new medicines are often conducted in an specialist clinical trial clinic, with dedicated pharmacologists, where the subject can be observed by full-time staff. These clinics are often run by a CRO who specialises in these studies.

At a participating site, one or more research assistants (often nurses) do most of the work in conducting the clinical trial. The research assistant's job can include some or all of the following: providing the local Institutional Review Board (IRB) with the documentation necessary to obtain its permission to conduct the study, assisting with study start-up, identifying eligible patients, obtaining consent from them or their families, administering study treatment(s), collecting and statistically analyzing data, maintaining and updating data files during followup, and communicating with the IRB, as well as the sponsor and CRO [10].

Ethical conduct

Clinical trials are closely supervised by appropriate regulatory authorities. All studies that involve a medical or therapeutic intervention on patients must be approved by a supervising ethics committee before permission is granted to run the trial. The local ethics

committee has discretion on how it will supervise noninterventional studies (observational studies or those using already collected data). In the U.S., 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 ensuring that 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.[21]

In some U.S. 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. International Conference of Harmonisation Guidelines for Good Clinical Practice (ICH GCP) is a set of standards used internationally for the conduct of clinical trials. The guidelines aim to ensure that 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, as for instance for questions of when to stop sequential treatments (see Odds algorithm), and then quantified methods may play an important role [11].
Additional ethical concerns are present when conducting clinical trials on children (pediatrics).

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 medical treatments. This allows the local investigators to make an informed judgment on whether to participate in the study or not.
- The sponsor is 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 U.S. as a Data Safety Monitoring Board). This is an independent group of clinicians and statisticians. The DMC meets periodically to review the unblinded data that 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 that "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

- A physician's first duty is to his/her patients, and if a physician investigator believes that 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 in order 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 responsible for ensuring that potential subjects in the study understand the risks and potential benefits of participating in the study; in other words, that they (or their legally authorized representatives) give truly informed consent.
- The local investigators 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). The local investigators 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 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 [12].
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IRBs

Approval by an IRB, or ethics board, is necessary before all but the most informal medical 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.
- In the U.S., 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.

Different countries have different regulatory requirements and enforcement abilities. "An estimated 40 percent of all clinical trials now take place in Asia, Eastern Europe, 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 [13].

ECONOMICS

Sponsor

The cost of a study depends on many factors, especially the number of sites that are 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 III or IV 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 onsite 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 that patients do not feel coerced to take part in the trial by overly attractive payments)

National health agencies such as the U.S. National Institutes of Health offer grants to investigators who design clinical trials that attempt to answer research questions that interest 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 [14].

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 in between clinical trials.

Subjects

In Phase I drug trials, participants are paid because they give up their time (sometimes away from their homes) and are exposed to unknown risks, without the expectation of any benefit. In most other trials, however, subjects are not paid, in order to ensure that 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 like travel or as compensation for their time in providing follow-up information about their health after they are discharged from medical care.

Participating in a clinical trial

Phase 0 and Phase I drug trials seek healthy volunteers. Most other clinical trials seek patients who have a specific disease or medical condition. There is general consensus that the diversity observed in society should be reflected in clinical trials through the appropriate inclusion of ethnic minority populations.

Locating trials

Depending on the kind of participants required, sponsors of clinical trials 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, people with Parkinson's disease can use PDtrials to find up-to-date information on Parkinson's disease trials currently enrolling participants in the U.S. and Canada, and search for specific Parkinson's clinical trials using criteria such as location, trial type, and symptom. 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 enrollment.

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 [15].

All volunteers being considered for a trial are required to undertake a medical screen. There are different requirements 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)

CONCLUSION

The last decade has seen a proliferation of information technology use in the planning and conduct of clinical trials. Clinical trial management systems (CTMS) are often used by research sponsors or CROs to help plan and manage the operational aspects of a clinical trial, particularly with respect to investigational sites. Web-based electronic data capture (EDC) and clinical data management systems (CDMS) are used in a majority of clinical trials to collect case report data from sites, manage its quality and prepare it for analysis. Interactive voice response systems (IVRS) are used by sites to register the enrollment of patients using a phone and to allocate patients to a particular treatment arm (although phones are being increasingly replaced with web-based (IWRS) tools which are sometimes part of the EDC system). Patient-reported outcome measures are being increasingly collected using hand-held, sometimes wireless ePRO (or eDiary) devices. Statistical software is used to analyze the collected data and prepare it for regulatory submission. Access to many of these applications are increasingly aggregated in web-based clinical trial portals.

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