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Review Article

A REVIEW: CLINICAL TRIAL AND DATA MANAGEMENT

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ABSTRACT

A clinical trial is a research study to answer specific questions about vaccines, new therapies or new ways of using known treatments. Clinical trials (also called medical research studies) are used to determine whether new drugs or treatments are both safe and effective. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people.

Keywords: Clinical trial protocol, Clinical studies, Clinical trial design, Data management.

INTRODUCTION

Clinical trials were first introduction in Avicenna"s The Canon of Medicine in 1025 AD, in which he laid down rules for the experimental use and testing of drugs and wrote a precise guide for practical experimental in the process of discovering and proving the effectiveness of medical drugs and substances.[1] He laid out the following rules and principle for testing the effectiveness of new drugs and medications, which still from the basic of modern clinical trials.[2, 3]

One of the most famous clinical trials was James Lind"s demonstration in 1747 that citrus fruits cure scurvy. He compound 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.[4] 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.

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.

Synonyms for „clinical trials‟ include clinical studies, research protocols and research. The most commonly performed clinical trials evaluate new drugs, medical device (like a new catheter), biologics, psychological therapies, or other interventions. Clinical trials may be required before the national regulatory authority will approve marketing of the drug or device, or a new dose of the drug, for use on patients.[5]

TYPES OF CLINICAL TRIAL

Clinical Trials

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, minerals, or lifestyle changes.

Screening trials

Test the best way to detect certain diseases or health conditions.

- 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 approved yet.
- 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).

Classifying Clinical Trials is By The Way the Researchers Behave

Diagnostics trials

Conduct to find better tests or procedures for diagnosing a particular disease or condition. In a clinical trial, the investigator first identifies the medication or be tested. Then the investigator decides what to compare it with (one or more existing treatment or a placebo), and what kind of patients might benefit from the medication /device.

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

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 for less than one year)

In an observational study, the investigators observe the subjects and measure their outcomes. The researchers do not actively manage the experiment. This is also called a natural experiment.

Treatment trials

Test experimental treatment, 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 (Supportive Care trials).

Compassionate use trials

Provide experimental therapeutics prior to final FDA approval to patients whose optional with other remedies have been unsuccessful. Usually, case by case approval must be granted by the FDA for such exceptions.

Community Based Clinical Trials

Community-based clinical trials are clinical trials conducted directly through doctors and clinics rather than academic research facilities. They are designed to be administered through primary care physicians, community health centers and local outpatient facilities. In 1986, the Community Consortium held the first such trials in the United States to determine the efficiacy of preventative treatments after the onset of Pneumocystis pneumonia[7]. The trials give patients access to new medications and keep doctors involved with new developments in research. However, critic‟s states that drugs company payment to doctors for patients enrolled in such studies present a conflict of interest and potential for abuse. Community-based trials are becoming prevalent in human-testing stage pharmaceutical research.[8, 9]

Randomized Controlled Trial

A randomized controlled trial (RCT) is a type of scientific experiment most commonly used in testing the efficacy or effectiveness of healthcare services (such as medicine or nursing) or health technologies (such as pharmaceuticals, medical devices or surgery). RCTs are also employed in other research areas, such as judicial, educational, and social research. As their name suggests, RCTs involve the random allocation of different interventions (treatments or conditions) to subjects. This ensures that both known and unknown confounding factors are evenly distributed between treatment groups. RCTs are considered the most reliable from of scientific evidence in healthcare because they eliminate spurious causality and bise.[10]

Types of Randomized Controlled Trial [11-14]

Open trial

Blind trial

- *Single-blind trial*
- *Double-blind trial*
- *Triple-blind trial*

Trials in healthcare

Aspects of control in clinical trials

Randomization in clinical trials

- *Randomization procedures*
  - *Complete randomization*
  - *Permuted block randomization*
  - *Urn randomization*
  - *Covariate-adaptive randomization*
  - *Outcome-adaptive randomization*
- *Allocation concealment*

Difficulties

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 randomized controlled trial. In observational studies, the investigators only observe associations (correlations) between the treatment 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 (I) and most phase (II) drug trials are designed as randomized, double blind, and placebo-controlled.[15]

Design Features

In designing a clinical trial, a sponsor must decide on the target number of patients who will participate. The sponsor‟s goal usually is to obtain a statistically significant result showing a significant difference in outcome (e.g., number of deaths after 28 days in the study) between the groups of patients who receive the study treatment. The number of patients required to give a statistically significant result depends on the question the trial wants to answer.

Phases

Clinical trials are conducted in phase. The trials at each phase have a different purpose and help scientists answer different questions:

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 phase 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 III are „post-approval" studies.[16]

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

Pre-clinical studies involve in vitro (i.e., test tube or laboratory) studies and trials on animal populations (in vivo). Wide-ranging dosages of the study drug are given to the animal subjects or to an in-vitro substrate in order to obtain preliminary efficacy, toxicity and pharmacokinetic information and to assist pharmaceutical companies in deciding whether it is worthwhile to go ahead with further testing.

- *Phase III*

Phase III studies are randomized controlled multicenter trials on large patient groups (300-3,000 or more depending upon the disease/medical condition studies) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current „gold standard" treatment. Because of their size and comparatively long duration, Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions.[18 19]

While not required in all cases, it is typically expected that there be at least two successful Phase III trials, demonstrating a drug"s safety and efficacy, in order to obtain approval from the appropriate regulatory agencies (FDA, USA); TGA, Australia and EMEA, European Union etc.).

Once a drug has proved satisfactory after Phase III trials, the trial results are usually combined into a large document containing a comprehensive description of the method and results of human and animal studies, manufacturing procedures, formulation details, and shelf life. This collection of information makes up the "regulatory submission" that is provided for review to the appropriate regulatory authorities in different countries. They will review the submission, and, it is hoped, give the sponsor approval to market the drug.[20]

Most drugs undergoing Phase III clinical trials can be marketed under FDA norms with proper

- *Phase 0*

Phase 0 is a recent designation for exploratory, first-in-human trials conducted in accordance with the U.S. Food and Drug Administration"s (FDA) 2006 Guidance on Exploratory Investigational New Drug (IND) Studies.[17]

- *Phase I*

Phase I trials are the first stage of testing in human subjects. Normally, a small (20-80) group of healthy volunteers will be selected. This phase includes trials designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug.

- *Phase II*

One the initial safety of the study drug has been confirmed in Phase I trials, Phase II trials are performed on larger groups (100-300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessment in a larger group of volunteers and patients. When the development process for a new drug fails, this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects.

recommendations and guidelines, but in case of any adverse effects being reported anywhere, the drugs need to be recalled immediately from the market. While most pharmaceutical companies refrain from this practice, it is not abnormal to see many undergoing Phase III clinical trials in the market. [21]

Phase IV

In these trials, post marketing studies delineate additional information including the drug‟s risks, benefits, and optimal use.

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 testing in a clinical trials. For example, a new cancer drug has, on average, at least 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.[22]

Administration

Clinical trials designed by a local investigator and (in the U.S.) federally funded clinical trials are almost always administered by the research who designed the study and applied for the grant. Small-scale device studies may be administered by the sponsoring company. Phase III and Phase IV 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

A Clinical Data Management System or CDMS is used in clinical research to manage the data of a clinical trial. The clinical trial data gathered at the investigator site in the case report form are stored in the CDMS. To reduce the possibility of errors due to human entry, the systems employ different means to verify the entry. The most popular method contracted to perform all the administrative work on a clinical trial. It 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 „clean‟ data from every site. Recently, site management organizations have also been hired to coordinate with the CRO to ensure rapid IRB/IEC approval and faster site initiation and patient recruitment and patient recruitment. [23]

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 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 Institutional Review Board (IRB). Most IRBs are located at the local investigator‟s hospital or institution, but some sponsors allow the use of a center (independent/for profit) IRB for investigators who work at smaller institutions.[23]

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.[23]

Accidents

In March 2006 the drug TGN1412 caused catastrophic systemic organ failure in the individuals receiving the drug during its first human clinical trials (Phase I) in Great Britain. Following this, an Expert Group on Phase One Clinical Trials published a report.[24]

Economics

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.[25]

CONTRACT RESEARCH ORGANIZATION

A Contract Research Organization (CRO) is an organization that offers clients a wide range of pharmaceutical research services. In the Code of Federal Regulations (CFR), the U.S. Food and Drug Administration regulations state that a CRO is "a person [i.e., a legal person, which may be a corporation] that assumes, as an independent contractor with the sponsor, one or the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation offered by materials to be the Food and Drug Administration".

Services offered by CROs include: product development and formulation, clinical trial management (preclinical through phase IV), central laboratory services for processing trial samples, data management services for preparation of an FDA New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA), and many other complementary services. CROs can offer their clients the experience of moving a new drug from its conception to FDA marketing approval without the drug sponsor having to maintain a staff for these services, which often have limited duration.[26]

PARTICIPATING IN A CLINICAL TRIAL

Newspapers, advertisement seeking patient and healthy volunteers to participate in clinical trials. Phase 0 and Phase I drug trials seek healthy volunteers. Most other clinical trials seek patients who have a specific disease or medical condition. 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.

CRO MARKET SIZE AND GROWTH

Global industry analysers estimated that pharmaceutical and biotechnology companies spent approximately $57 billion R & D in 2005, out of which an estimated $14 billion was used for the outsourcing services offered by the CRO industry. This figure is expected to increase further with the broadening of the spectrum of services outsourced to cover the entire value chain. As the outsourced services to China and India move up the value chain to cover phase 1/2 trials, the total contracts value may go up to $20 billion by 2010.

A Contract Research Organization (CRO) is a type of organization that offers a wide range of pharmaceutical drug biologic and device development services. These services can include: product and process development, toxicology, clinical trial management from Phase I to Phase IV (including study startup, monitoring and closeout), data management, and biostatistics, medical writing and regulatory affairs (including consultations and regulator submission). An eCRO provide all of the above services, but has developed their own electronic tools to support the drug, biologic and device development processes. These tools include:

web-based document management (including access and version control, as well as electronic signatures), clinical trial management system (CTMS), autoencoding of adverse events (MedDRA), and concomitant medications (WHO DRUG), and electronic data capture (EDC) which eliminates double-key data entry. Other tools can include mapping to CDISE, electronic newsletters, eCTD preparation for IND and NDA, etc.

CLINICAL TRIAL MANAGEMENT

A clinical trial is the application of the scientific method to human health. Since such trials require the use of human test subjects and can severely impact the well-being of the subjects, as well as treatments of other people and large amounts of capital for those performing the trial, the proper management of clinical trials is crucial.[27,28]

CLINICAL TRIAL MANAGEMENT SYSTEM

A Clinical Trial Management System, also known as CTMS, is a customizable software system used by the biotechnology and pharmaceutical industries to manage the large amounts of data involved with the operation, of a clinical trial. It maintains and manages the planning, preparation performance, and reporting of clinical trials, with emphasis on keeping up-to-date contact information for participants and tracking deadliness and milestones such as those for regulatory approval or the issue of progress reports. Often, a clinical trial management system provides data to a business intelligence system, which acts as a digital dashboard for trial managers.

In the early phases of clinical trial, when the number of patients and tests are small, most managers use an in-house or home-grown program to handle their data. As the amount of data grows, though, organizations increasingly look to replace their system with more stable, feature-rich software provided by specialized vendors. Each manager has different requirements that a system must satisfy. Some popular requirements include: budgeting, patient management, compliance with government regulations, and compatibility with other data management systems.[29]

Each sponsor has different requirements that their CTMS must satisfy; it would be impossible to create a complete list of CTMS requirements. Despite differences, several requirements are pervasive, including: project management, EC/IRB approvals, compliance with FDA regulations, and compatibility with other system such as data management systems, electronic data capture, and adverse event reporting systems.[30]

CLINICAL DATA MANAGEMENT SYSTEM

Double data entry at the end of the clinical trial the dataset in the CDMS is analyzed and sent to the regulatory authorities for approval.[31-33]

CLINICAL TRIAL DATA MANAGEMENT

Data management comprises all the disciplines related to managing data as a valuable resource. The official definition provided by DAMA is that “Data Resource Management is the development and execution of architectures, policies, practices and procedures that properly manage the full data lifecycle needs of an enterprise”. The definition is fairly broad and encompasses a number of professions which may not have direct technical contact with lower-level aspects of data management, such as relational database management. Alternatively, the definition provided in the DAMA Data Management Body of knowledge (DAMA-DMBOK) is: “Data management is the development, execution and supervision of plans, policies, programs and practices that control, deliver and enhance the value of data information assets”. [34,35]

CONCLUSION

After a clinical trial is completed, the researchers look carefully at the data collected during the trial before making decisions about the findings and further testing. After a phase I or II trial, the researchers decide whether to move on to the next phase, or stop testing the agent or intervention because it was not safe or effective. When a phase III trial is completed, the researchers look at the data and decide whether the results have medical importance.

The results of clinical trials are often published in peer-reviewed, scientific journals. Peer reviewed, scientific journals, Peer review is a process by which experts review the report before it is published to make sure the analysis and conclusions are sound. If the results are particularly important, they may be featured by the media and discussed at scientific meetings and by patient advocacy groups before they are published. Once a new approach has been proven safe and effective in a clinical trial, it may become standard practice.

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