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Review

Role Of Post Approval Clinical Trials For Drug Safety

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Abstract

In Pharmaceutical Industry, Regulatory Affairs Department makes an interface between the regulatory authorities and pharmaceutical industry. The Regulatory Affairs department is an important part of the organizational structure of pharmaceutical companies. Internally it liaises at the inter phase of drug development, manufacturing, marketing and clinical research. Externally it is the key interface between the company and the regulatory authorities. Regulatory Affairs is involved in the development of new medicinal products from early on, by integrating regulatory principles and by preparing and submitting the relevant regulatory dossiers to health authorities. Regulatory Affairs is actively involved in every stage of development of a new medicine and in the post-marketing activities with authorized medicinal products. This professional can play a key role in guiding drug development strategy in an increasingly global environment and has an important role for submitting the newly discovered drug products approval documents to the US FDA regulatory authorities and to carry out all the practices required for obtaining the drug products approval. This article mainly focuses on the US FDA drug approval strategies. These strategies playing core job in the pharmaceutical industry. These strategies having all the guidelines which are indispensable part of the IND, NDA and ANDA drug approval applications. It plays a significant role in sequence for registration of newly exposed products and also providing the guidelines which is helpful preparing the registration documents to regulatory authorities.

Keywords: Post Approval, Post marketing, Pharmacodynamics, pharmacokinetics

INTRODUCTION

Clinical Trial Introduction

Monitoring patient safety during a clinical trial is one of the founding principles to be followed throughout the drug development life cycle. It can be defined as a collaborative relationship between sponsors, sites, researchers, and everyone involved in the clinical trial phases.

Clinical trials are experiments or observations done in clinical research. Such prospective biomedical or behavioral research studies on human participants are designed to answer specific questions about biomedical or behavioral interventions, including new treatments (such as novel vaccines, drugs, dietary choices, dietary supplements, and medical devices) and known interventions that warrant further study and comparison. Clinical trials generate data on dosage, safety and efficacy.1 They are conducted only after they have received health authority/ethics committee approval in the country where approval of the therapy is sought. These authorities are responsible for vetting the risk/benefit ratio of the trial—their approval does not mean the therapy is 'safe' or effective, only that the trial may be conducted.

Depending on product type and development stage, investigators initially enroll volunteers or patients into small pilot studies, and subsequently conduct progressively larger scale comparative studies. Clinical trials can vary in size and cost, and they can involve a single research center or multiple centers, in one country or in multiple countries. Clinical study design aims to ensure the scientific validity and reproducibility of the results.
Costs for clinical trials can range into the billions of dollars per approved drug.2 The sponsor may be a governmental organization or a pharmaceutical, biotechnology or medical device company. Certain functions necessary to the trial, such as monitoring and lab work, may be managed by an outsourced partner, such as a contract research organization or a central laboratory. Only 10 percent of all drugs started in human clinical trials become approved drugs.3

Trials of drugs

Some clinical trials involve healthy subjects with no pre-existing medical conditions. Other clinical trials pertain to people with specific health conditions who are willing to try an experimental treatment. Pilot experiments are conducted to gain insights for design of the clinical trial to follow.

There are two goals to testing medical treatments: to learn whether they work well enough, called "efficacy" or "effectiveness"; and to learn whether they are safe enough, called "safety". Neither is an absolute criterion; both safety and efficacy are evaluated relative to how the treatment is intended to be used, what other treatments are available, and the severity of the disease or condition. The benefits must outweigh the risks.4,5
For example, many drugs to treat cancer have severe side effects that would not be acceptable for an over-the-counter pain medication, yet the cancer drugs have been approved since they are used under a physician's care and are used for a life-threatening condition.6

In the US, the elderly constitute 14% of the population, while they consume over one-third of drugs.7 People over 55 (or a similar cutoff age) are often excluded from trials because their greater health issues and drug use complicate data interpretation, and because they have different physiological capacity than younger people. Children and people with unrelated medical conditions are also frequently excluded.8 Pregnant women are often excluded due to potential risks to the fetus.

The sponsor designs the trial in coordination with a panel of expert clinical investigators, including what alternative or existing treatments to compare to the new drug and what type(s) of patients might benefit. If the sponsor cannot obtain enough test subjects at one location investigators at other locations are recruited to join the study.

During the trial, investigators recruit subjects with the predetermined characteristics, administer the treatment(s) and collect data on the subjects' health for a defined time period. Data include measurements such as vital signs, concentration of the study drug in the blood or tissues, changes to symptoms, and whether improvement or worsening of the condition targeted by the study drug occurs. The researchers send the data to the trial sponsor, who then analyzes the pooled data using statistical tests.
Examples of clinical trial goals include assessing the safety and relative effectiveness of a medication or device:
On a specific kind of patient
At varying dosages
For a new indication

Evaluation for improved efficacy in treating a condition as compared to the standard therapy for that condition. Evaluation of the study drug or device relative to two or more already approved/common interventions for that condition. While most clinical trials test one alternative to the novel intervention, some expand to three or four and may include a placebo. Except for small, single-location trials, the design and objectives are specified in a document called a clinical trial protocol. The protocol is the trial's "operating manual" and ensures all researchers perform the trial in the same way on similar subjects and that the data is comparable across all subjects. As a trial is designed to test hypotheses and rigorously monitor and assess outcomes, it can be seen as an application of the scientific method, specifically the experimental step. The most common clinical trials evaluate new pharmaceutical products, medical devices, biologics, psychological therapies, or other interventions. Clinical trials may be required before a national regulatory authority9 approves marketing of the innovation.

Trials of devices

Similarly to drugs, manufacturers of medical devices in the United States are required to conduct clinical trials for premarket approval.10 Device trials may compare a new device to an established therapy, or may

compare similar devices to each other. An example of the former in the field of vascular surgery is the Open versus Endovascular Repair (OVER trial) for the treatment of abdominal aortic aneurysm, which compared the older open aortic repair technique to the newer endovascular aneurysm repair device.11 An example of the latter are clinical trials on mechanical devices used in the management of adult female urinary incontinence.12

Trials of procedures

Similarly to drugs, medical or surgical procedures may be subjected to clinical trials,13 such as case-controlled studies for surgical interventions.13

History

The concepts behind clinical trials are ancient. The Book of Daniel chapter 1, verses 12 through 15, for instance, describes a planned experiment with both baseline and follow-up observations of two groups who either partook of, or did not partake of, "the King's meat" over a trial period of ten days. Persian physician Avicenna, in The Canon of Medicine (1025) gave similar advice for determining the efficacy of medical drugs and substances.15

Development

Edward Jenner vaccinating James Phipps, a boy of eight, on 14 May 1796. Jenner failed to use a control group. Although early medical experimentation was performed often, the use of a control group to provide an accurate comparison for the demonstration of the intervention's efficacy was generally lacking. For instance, Lady Mary Wortley Montagu, who campaigned for the introduction of inoculation (then called variolation) to prevent smallpox, arranged for seven prisoners who had been sentenced to death to undergo variolation in exchange for their life. Although they survived and did not contract smallpox, there was no control group to assess whether this result was due to the inoculation or some other factor. Similar experiments performed by Edward Jenner over his smallpox vaccine were equally conceptually flawed.15

The first proper clinical trial was conducted by the Scottish physician James Lind.16 The disease scurvy, now known to be caused by a Vitamin C deficiency, would often have terrible effects on the welfare of the crew of long-distance ocean voyages. In 1740, the catastrophic result of Anson's circumnavigation attracted much attention in Europe; out of 1900 men, 1400 had died, most of them allegedly from having contracted scurvy.17 John Woodall, an English military surgeon of the British East India Company, had recommended the consumption of citrus fruit (it has an antiscorbutic effect) from the 17th century, but their use did not become widespread.18

Lind conducted the first systematic clinical trial in 1747.19 He included a dietary supplement of an acidic quality in the experiment after two months at sea, when the ship was already afflicted with scurvy. He divided twelve scorbutic sailors into six groups of two. They all received the same diet but, in addition, group one was given a quart of cider daily, group two twenty-five drops of elixir of vitriol (sulfuric acid), group three six spoonfuls of vinegar, group four half a pint of seawater, group five received two oranges and one lemon, and the last group a spicy paste plus a drink of barley water. The treatment of group five stopped after six days when they ran out of fruit, but by then one sailor was fit for duty while the other had almost recovered. Apart from that, only group one also showed some effect of its treatment.20

After 1750, the discipline began to take its modern shape.21,22 The English doctor John Haygarth demonstrated the importance of a control group for the correct identification of the placebo effect in his celebrated study of the ineffective remedy called Perkin's tractors. Further work in that direction was carried out by the eminent physician Sir William Gull, 1st Baronet in the 1860s.15

Frederick Akbar Mahomed (d. 1884), who worked at Guy's Hospital in London, made substantial contributions to the process of clinical trials, 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."23

Types of Clinical Trials

Clinical trials are classified by the research objective created by the investigators.29 In an observational study, the investigators observe the subjects and measure their outcomes. The researchers do not actively manage the study.30 In an interventional study, the investigators give the research subjects an experimental drug, surgical procedure, use of a medical device, diagnostic or other intervention to compare the treated subjects with those receiving no treatment or the standard treatment. Then the researchers assess how the subjects' health changes.30 Trials are classified by their purpose. After approval for human research is granted to the trial sponsor, the U.S. Food and Drug Administration (FDA) organizes and monitors the results of trials according to type:29 Prevention trials look for ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include drugs, vitamins or other micronutrients, vaccines, or lifestyle changes. Screening trials test for ways to identify certain diseases or health conditions. Diagnostic trials are conducted to find better tests or procedures for diagnosing a particular disease or condition. Treatment trials test experimental drugs, new combinations of drugs, or new approaches to surgery or radiation therapy. Quality of life trials

(supportive care trials) evaluate how to improve comfort and quality of care for people with a chronic illness. Genetic trials are conducted to assess the prediction accuracy of genetic disorders making a person more or less likely to develop a disease. Epidemiological trials have the goal of identifying the general causes, patterns or control of diseases in large numbers of people.

Compassionate use trials or expanded access trials provide partially tested, unapproved therapeutics to a small number of patients who have no other realistic options. Usually, this involves a disease for which no effective therapy has been approved, or a patient who has already failed all standard treatments and whose health is too compromised to qualify for participation in randomized clinical trials.31 Usually, case-by-case approval must be granted by both the FDA and the pharmaceutical company for such exceptions.

Fixed trials consider existing data only during the trial's design, do not modify the trial after it begins, and do not assess the results until the study is completed.

Adaptive clinical trials use existing data to design the trial, and then use interim results to modify the trial as it proceeds. Modifications include dosage, sample size, drug undergoing trial, patient selection criteria and "cocktail" mix.32 Adaptive trials often employ a Bayesian experimental design to assess the trial's progress. In some cases, trials have become an ongoing process that regularly adds and drops therapies and patient groups as more information is gained.33 The aim is to more quickly identify drugs that have a therapeutic effect and to zero in on patient populations for whom the drug is appropriate.[34,35] Clinical trials are conducted typically in four phases, with each phase using different numbers of subjects and having a different purpose to construct focus on identifying a specific effect.[29]

Phases

National Cancer Institute video on the phases of clinical trials

Clinical trials involving new drugs are commonly classified into five phases. Each phase of the drug approval process is treated as a separate clinical trial. The drug development process will normally proceed through phases I–IV over many years, frequently involving a decade or longer. 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.29 Phase IV trials are performed after the newly approved drug, diagnostic or device is marketed, providing assessment about risks, benefits, or best uses.29

Single subtherapeutic doses of the study drug or treatment are given to a small number of subjects (typically 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).36 For a test drug, the trial documents the absorption, distribution, metabolization, and clearance (excretion) of the drug, and the drug's interactions within the body, to confirm that these appear to be as expected.

Phase I: Screening for safety Often are first-in-person trials. Testing within a small group of people (typically 20–80) to evaluate safety, determine safe dosage ranges, and identify side effects.[29]

Phase II: Establishing the preliminary efficacy of the drug in a "treatment group", usually against a placebo control group

Phase IIa: is specifically designed to assess dosing requirements (how much drug should be given),29,37 while a Phase IIb: trial is designed to determine efficacy, and studies how well the drug works at the prescribed dose(s), establishing a therapeutic dose range.[37]

Phase III: Final confirmation of safety and efficacy Testing with large groups of people (typically 1,000–3,000) to confirm its efficacy, evaluate its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely.[29]

Phase IV: Safety studies during sales Post marketing studies delineate risks, benefits, and optimal use. As such, they are ongoing during the drug's lifetime of active medical use.[29]

Trial 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.

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.

Phases of clinical research28

The phases of clinical research are the steps in which scientists do experiments with a health intervention in an attempt to find enough evidence for a process which would be useful as a medical treatment. In the case of pharmaceutical study, the phases start with drug design and drug discovery, go on to animal testing, then start by testing in only a few human subjects and expand to test in many study participants if the trial seems safe and useful

Phases

Clinical trials involving new drugs are commonly classified into four phases. Clinical trials of drugs may not fit into a single phase. For example, some may blend from phase I to phase II or from phase II to phase III. Therefore, it may be easier to think of early phase studies and late phase studies. 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 IV are 'post-approval' studies.

CONCLUSION

The quantity and quality of postapproval clinical evidence varied substantially for novel drugs first approved by the FDA on the basis of limited evidence, with few controlled studies published after approval that confirmed efficacy using clinical outcomes for the original FDA approved indication. Drug safety is a major public health concern, especially in today's society with vast amounts of new drugs coming onto the market. And no drug is perfectly safe; however, it is possible to improve the post-market drug surveillance system so that people are only exposed to those drugs that have benefits outweighing their health risks. Congress and officials at the FDA need to take a look at the process and be willing to commit to the FDAAA changes to improve post-market drug safety. With the current rates of ADEs and poor reporting, the nation cannot afford for the post-market drug surveillance system to lag behind. The FDA keeps trying small changes to the system, but these simply are not enough. A major overhaul needs to happen so that this imperative public health concern is properly protected.

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