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Review Article

"CLINICAL TRIALS IN INDIA"

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ABSTRACT

The larger context of clinical trials in India is poverty and the absence of affordable healthcare. For more than a decade, government policy has been to reduce public support for healthcare services, and these services are under-resourced. Health economists have pointed out that only 15 per cent of the Rs 1,500 billion spent in the health sector in India comes from the government. 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. 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. The level of concern about the impact of the CTD on clinical research activities is intense and widespread overall stakeholder groups. Opinions and quantitative survey results draw a picture of increased bureaucracy and costs, reduction of important research without creating benefits for patients. However, concrete, comprehensive figures about the clinical trial activities are only available from competent authorities. Figures on the CTD's impact on organisation, staffing, costs and processes of the different stakeholders are missing.These trials violated the the Indian Council of Medical Research's Ethical guidelines for biomedical research on human subjects and the World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. The trial designs do not seem to have violated regulations for the conduct of clinical research in India. The existing regulatory apparatus therefore permits unethical trials of no benefit to Indians. Clearly, trials are being conducted in India that could not be conducted in developed countries, taking advantage of people's lack of access to affordable, good quality care.

The benefits of research do not reach the community as drugs found effective following these trials may not be affordable to the community in which they were tested. Such practices are in violation of the Declaration of Helsinki as well as the general principles laid down in the Indian Council of Medical Research's ethical guidelines for biomedical research.The infrastructure for regulation, ethics review and monitoring is insufficient. The government's priority seems to be ensuring that clinical research in India produces good quality data according to Good Clinical Practice standards. Ethical guidelines – including its own ethical guidelines – seem to be of secondary importance. The ethical concerns raised by these clinical trials; the weak regulatory apparatus to protect trial participants, government policy to encourage international clinical trials without taking active steps to put in place a system to protect participants from harm; people's desperation for affordable health care – all this will only worsen the harm being done to trial participants in India.tum since the dis

Keywords: clinical trials, Pre-clinical trials, NDA Process, Safety of Clinical Trial, Unethical Trials in India

INTRODUCTION

A clinical trial is a research study in human subjects with the aim of answering specific questions about a new medical treatment (vaccines, new therapies or new ways of using known treatments). Clinical trials (also called medical research and research studies) are used to determine whether new drugs or treatments are both safe and effective. Pharmaceutical clinical trials are conducted in Phases.

The trials at each Phase have a different purpose and each Phase looks at different areas (e.g. toxicity, dose finding etc) Clinical trials often involve patients with specific health conditions who then benefit from receiving 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 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 (Avorn, 2004). Despite this, they are often excluded from trials because their more frequent health issues and drug use produces unreliable data. Women, children, and people with unrelated medical conditions are also frequently excluded (Van at el., 2007). 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. If the sponsor cannot obtain enough patients with this specific disease or condition at one location, then investigators at other locations who can obtain the same kind of patients to receive the treatment would be recruited into the study. 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 voluntaries 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.

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 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. 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." Trial is from the Anglo–French Trier, meaning to try. Broadly, it refers to the action or process of putting something to a test or proof.

Clinical is from clinic, from the French cliniqu´e and from the Greek klinike, and refers to the practice of caring for the sick at the be dside. Hence, narrowly, a clinical trial is the action or process of putting something to a test or proof at the bedside of the sick. However, broadly it refers to any testing done on human beings for the sake of determining the value of a treatment for the sick or for preventing disease or sickness.

The concepts behind clinical trials, however, are ancient. The Book of Daniel 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.[9] 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.[10] He laid out the following rules and principles for testing the effectiveness of new drugs and medications: [11][12]

- The drug must be free from any extraneous accidental quality.
- It must be used on a simple, not a composite, disease.
- 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.
- 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.
- The time of action must be observed, so that essence and accident are not confused.
- 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.
- 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.[13]

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 (d. 1884), who worked at Guy's Hospital in London,[14] 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."[15]

TYPE OF CLINICAL TRIAL

There are several types of 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, vaccines, minerals, or lifestyle changes. Prevention trials test new approaches, such as medications,vitamins, or other supplements, that doctors believe may lower the risk of developing a certain type of cancer. Most prevention trials are conducted with healthy people who have not had cancer. Some trials are conducted with people who have had cancer and want to prevent recurrence (return of cancer), or reduce the chance of developing a new type of cancer.

Screening trials

test the best way to detect certain diseases or health conditions. Screening trials study ways to detect cancer earlier. They are often conducted to determine whether finding cancer before it causes symptoms decreases the chance of dying from the disease. These trials involve people who do not have any symptoms of cancer.

Diagnostic trials

conducted to find better tests or procedures for diagnosing a particular disease or condition. Diagnostic trialsstudy tests or procedures that could be used to identify cancer more accurately. Diagnostic trials usually include people who have signs or symptoms of cancer.

Treatment trials

Test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy. Treatment trials are conducted with people who have cancer. They are designed to answer specific questions about, and evaluate the effectiveness of, a new treatment or a new way of using astandard treatment. These trials test many types of treatments, such as new drugs, vaccines, new approaches to surgery orradiation therapy, or new combinations of treatments.

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). Quality-of-life (also called supportive care) trials explore ways to improve the comfort and quality of life of cancer patients and cancer

survivors. These trials may study ways to help people who are experiencing nausea, vomiting, sleep disorders,depression, or other effects from cancer or its treatment.

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.

Genetics studies are sometimes part of another cancer clinical trial. The genetics component of the trial may focus on how geneticmakeup can affect detection, diagnosis, or response to cancer treatment.

DESIGN OF CLINICAL STUDY

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.

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".[19]

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

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., improvement percentage in the treatment of psoriasis using hydrocortisone after 42 days).[20] Between the groups of patients who receive the study treatment and those who receive a placebo or a different treatment.

The number of patients required to give a statistically significant result depends on the question the trial wants to answer. For example, to show the effectiveness of a new drug in a non-curable disease as metastatic kidney cancer requires many fewer patients than in a highly curable disease as seminoma if the drug is compared to a placebo.

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 .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 .70 to detect a difference of 5 mg/dL.

PHASES OF CLINICAL TRIALS

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 IV are 'post-approval' studies.

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

Pre-clinical studies

Pre-clinical studies involve in vitro (test tube or cell culture) and in vivo (animal) experiments using wide-ranging doses of the study drug to obtain preliminary efficacy, toxicity and pharmacokinetic information. Such tests assist pharmaceutical companies to decide whether a drug candidate has scientific merit for further development as an investigational new drug.

Phase 0

Phase 0 is a recent designation for exploratory, first-in-human trials conducted in accordance with the United States Food and Drug Administration's (FDA) 2006 Guidance on Exploratory Investigational New Drug (IND) Studies.[21]

Phase 0 trials are also known as human microdosing studies and are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in human subjects as was expected from preclinical studies.

Distinctive features of Phase 0 trials include the administration of single subtherapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics (how the body processes the drug) and pharmacodynamics (how the drug works in the body).[22]

A Phase 0 study gives no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect. Drug development companies carry out Phase 0 studies to rank drug candidates in order to decide which has the best pharmacokinetic parameters in humans to take forward into further development. They enable go/no-go decisions to be based on relevant human models instead of relying on sometimes inconsistent animal data.

Questions have been raised by experts about whether Phase 0 trials are useful, ethically acceptable, feasible, speed up the drug development process or save money, and whether there is room for improvement.[23]

Phase I

Phase I trials are the first stage of testing in human subjects. Normally, a small (20-100) group of healthy volunteers will be selected. This phase includes trials designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug.

These trials are often conducted in an inpatient clinic, where the subject can be observed by full-time staff. The subject who receives the drug is usually observed until several half-lives of the drug have passed. Phase I trials also normally include dose-ranging, also called dose escalation, studies so that the appropriate dose for therapeutic use can be found.

The tested range of doses will usually be a fraction of the dose that causes harm in animal testing. Phase I trials most often include healthy volunteers. However, there are some circumstances when real patients are used, such as patients who have terminal cancer or HIV and lack other treatment options. Volunteers are paid an inconvenience fee for their time spent in the volunteer centre.

There are different kinds of Phase I trials

SAD: Single Ascending Dose studies are those in which small groups of subjects are given a single dose of the drug while they are observed and tested for a period of time. If they do not exhibit any adverse side effects, and the pharmacokinetic data is roughly in line with predicted safe values, the dose is escalated, and a new group of subjects is then given a higher dose. This is continued until pre-calculated pharmacokinetic safety levels are reached, or intolerable side effects start showing up (at which point the drug is said to have reached the Maximum tolerated dose (MTD).

MAD: Multiple Ascending Dose studies are conducted to better understand the pharmacokinetics & pharmacodynamics of multiple doses of the drug. In these studies, a group of patients receives multiple low doses of the drug, while samples (of blood, and other fluids) are collected at various time points and analyzed to understand how the drug is processed within the body. The dose is subsequently escalated for further groups, up to a predetermined level. Food effect a short trial designed to investigate any differences in absorption of the drug by the body, caused by eating before the drug is given. These studies are usually run as a crossover study, with volunteers being given two identical doses of the drug on different occasions; one while fasted, and one after being fed.

Phase II

Once the initial safety of the study drug has been confirmed in Phase I trials, Phase II trials are performed on larger groups (20-300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments 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.

Phase II studies are sometimes divided into Phase IIA and Phase IIB.

Phase IIA is specifically designed to assess dosing requirements (how much drug should be given).

Phase IIB is specifically designed to study efficacy (how well the drug works at the prescribed dose(s)).

Some trials combine Phase I and Phase II, and test both efficacy and toxicity.

Trial design: Some Phase II trials are designed as case series, demonstrating a drug's safety and activity in a selected group of patients. Other Phase II trials are designed as randomized clinical trials, where some patients receive the drug/device and others receive placebo/standard treatment. Randomized Phase II trials have far fewer patients than randomized Phase III trials.

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 studied) 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.

It is common practice that certain Phase III trials will continue while the regulatory submission is pending at the appropriate regulatory agency.

This allows patients to continue to receive possibly lifesaving drugs until the drug can be obtained by purchase. Other reasons for performing trials at this stage include attempts by the sponsor at "label expansion" (to show the drug works for additional types of patients/diseases beyond the original use for which the drug was approved for marketing), to obtain additional safety data, or to support marketing claims for the drug. Studies in this phase are by some companies categorised as "Phase IIIB studies."[24][25] 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 such as FDA (USA), or the EMA (European Union), for example.

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 methods 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 [4] in different countries. They will review the submission, and, it is hoped, give the sponsor approval to market the drug.

Most drugs undergoing Phase III clinical trials can be marketed under FDA norms with proper 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 drugs undergoing Phase III clinical trials in the market.[26]

Phase IV

Phase IV trial is also known as Post Marketing Surveillance Trial. Phase IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold. Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I-III clinical trials. Harmful effects discovered by Phase IV trials may result in a drug being no longer sold, or restricted to certain uses: recent examples involve cerivastatin (brand names Baycol and Lipobay), troglitazone (Rezulin) and rofecoxib (Vioxx).

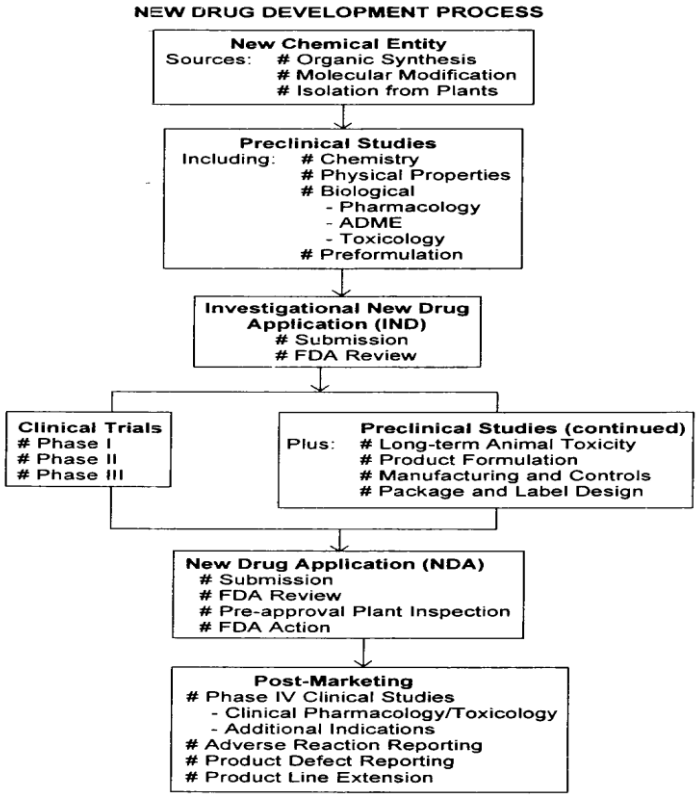


Fig. 2.1 Schematic representation of new drug development process, from drug discovery, through preclinical and clinical studies, new drug application and postmarketing activities. (FDA = Food anc Drug Administration as in USA).

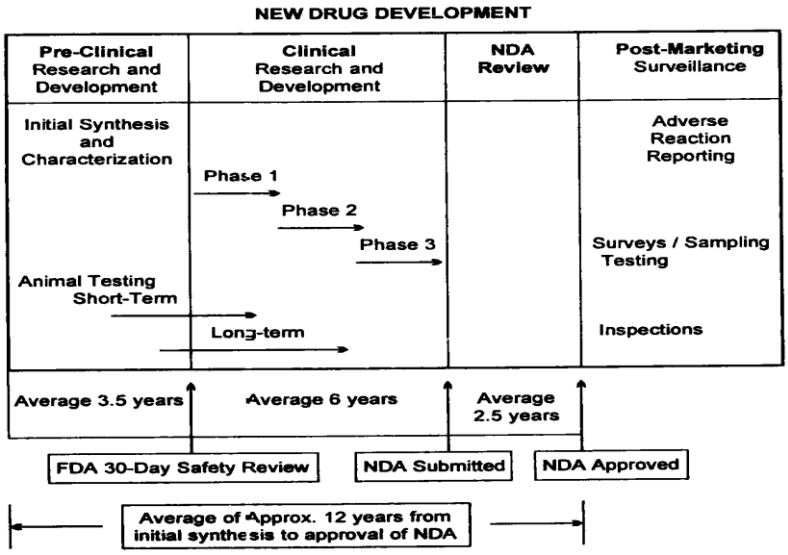


Fig. 2.2 The time-course of development and testing processes required to bring a new drug to market.

ADMINISTRATION STUDY

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. 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 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.

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.

ETHICAL CONDUCT OF CLINICAL TRIAL

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.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.Additional ethical concerns are present when conducting clinical trials on children (pediatrics).

Ethical guidelines for biomedical research

As of January 2005, biomedical research in India must comply with the ethical principles laid out in the World Medical Association Declaration of Helsinki. It must also follow the the Indian Council of Medical Research's ethical guidelines for biomedical research on humans.

World Medical Association Declaration of Helsinki

The Declaration of Helsinki is accepted as an international standard for biomedical research. The Declaration has been revised a number of times since it was first adopted by the World Medical Association's General Assembly in June 1964. The Declaration of Helsinki was last revised on October 22, 200825 and is the relevant document for ongoing and future research. The trials described in this report took place between 2002 and 2006. The following paragraphs, on research among vulnerable groups, the informed consent process, the use of placebo controls and the benefits of research are particularly relevant in these trials.

The economically and medically disadvantaged need special protection: Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

Investigator/physicians recruiting their patients into a clinical trial must be careful not to exercise undue influence: When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a wellinformed physician who is not engaged in the investigation and who is completely independent of this relationship.

Placebos or sugar pills should not be used when testing new drugs if an effective treatment for that condition already exists: The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.25 World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Adopted by the WMA General Assembly, Helsinki, Finland, June 1964 and lastamended at the 59th WMA Assembly, Seoul, October 2008. Available from: Ethical concerns in clinical trials in India: an investigation

The Indian Council of Medical Research's ethical guidelines onbiomedical research on humans

As of January 2005, it is mandatory for clinical trials in India to conform to the ICMR'sguidelines and to the guidelines in the Declaration of Helsinki. The Indian Council of Medical Research's guidelines were first published in 200026 and this version of the guidelines would have been applicable for the trials described in this report. The revised guidelines were published in 200627 and are the relevant guidelines for ongoing and future research. The guidelines state that: "persons who are economically or socially disadvantaged should not be used to benefit those who are better off than them." (Section III iii b in ICMR, 2000; 27 Indian Council of Medical Research. Ethical guidelines for biomedical research on human participants. New Delhi: ICMR; 2006. Available from: Ethical concerns in clinical trials in India: an investigation 'Any research using the [sic] human beings should be selected so that burdens and benefits of the research are distributed without arbitrariness, discrimination or caprice." Research should abide by the principles of "maximisation of the public interest and of distributive justice

whereby, the research or experiment and its subsequent applicative use are conducted and used to benefit all humankind and not just those who are socially better off but also the least advantaged; and in particular the research subject themselves.

SAFETY OF CLINICAL TRIAL

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.[30]

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.NThe local investigator is responsible for being truthful to the local IRB in all communications relating to the study.

IRB

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." [31]

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.[32] Investigational drug Trovan was tested on children in Nigeria causing severe health problems leading to lawsuits.[33] In May 2010, a Phase III clinical trial for rheumatoid arthritis using ocrelizumab, an investigational new drug sponsored by Roche and Biogen Idec, was shut down after an excess number of deaths due to opportunistic infections in the interventional arm of the study.[34] In October 2010, a Phase II trial for multiple sclerosis using the same drug was shut down after a patient died from systemic inflammatory response syndrome while taking the drug.[35][36]

ECONOMICS AND PARTICIPATING IN CLINICAL TRIAL

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)

In the U.S. there is a 50% tax credit for sponsors of certain clinical trials.[37] 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.[38]

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.

Patients

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, patients 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

Newspaper advertisements seeking patients 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.

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.[39] Other disease-specific services exist for volunteers to find trials related to their condition.[40] Volunteers may also 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.[citation needed]

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.[41]

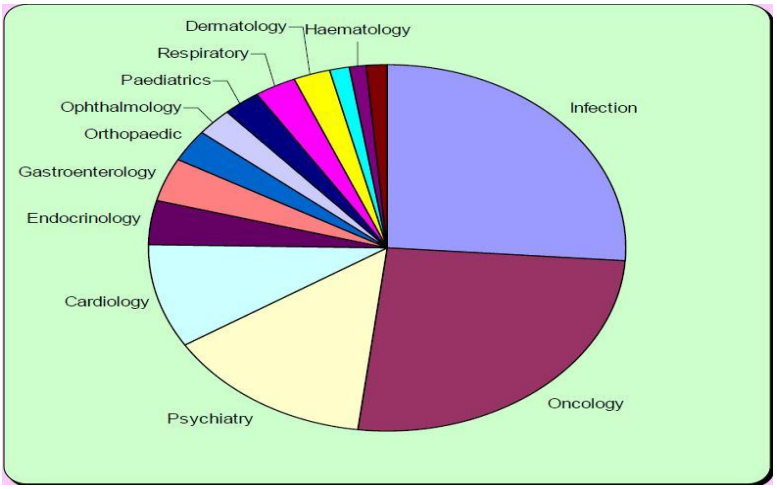
All volunteers being considered for a trial are required to undertake a medical screen. There are different requirements for different trials, but typically volunteers will have the following tests:[42]

- 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)

INFORMATION TECHNOLOGY IN CLINICAL TRIAL

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 [43] 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 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.

Clinical Trial Experiance



CRITICISM OF CLINIAL TRIAL

Marcia Angell has been a stern critic of U.S. health care in general and the pharmaceutical industry in particular. She is scathing on the topic of how clinical trials are conducted in America:Many drugs that are assumed to be effective are probably little better than placebos, but there is no way to know because negative results are hidden.... Because favorable results were published and unfavorable results buried ... the public and the medical profession believed these drugs were potent.... Clinical trials are also biased through designs for research that are chosen to yield favorable results for sponsors. For example, the sponsor's drug may be compared with another drug administered at a dose so low that the sponsor's drug looks more powerful.

Or a drug that is likely to be used by older people will be tested in young people, so that side effects are less likely to emerge. A common form of bias stems from the standard practice of comparing a new drug with a placebo, when the relevant question is how it compares with an existing drug.

In short, it is often possible to make clinical trials come out pretty much any way you want, which is why it's so important that investigators be truly disinterested in the outcome of their work.... It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of the New England Journal of Medicine.[44]

Angell believes that members of medical school faculties who conduct clinical trials should not accept any payments from drug companies except research support, and that support should have no strings attached, including control by the companies over the design, interpretation, and publication of research results.She has speculated that "perhaps most" of the clinical trials are viewed by critics as "excuses to pay doctors to put patients on a company's already-approved drug".[45]

CLINIAL TRIALS IN INDIA

The larger context of clinical trials in India is poverty and the absence of affordable healthcare. For more than a decade, government policy has been to reduce public support for healthcare services, and these services are under-resourced. Health economists have pointed out that only 15 per cent of the Rs 1,500 billion spent in the health sector in India comes from the government. Four per cent comes from social insurance and one per cent from private insurance companies. The remaining 80 per cent is spent by individuals using private services and without insurance.

Two-thirds of health care users bear 100 per cent of their health care expenses. Seventy per cent of these health care users are poor. More than half of the poorest 20 per cent of Indians sold assets or borrowed to pay for health care4. Patients in both government hospitals and private hospitals are desperate for better quality and affordable care. Patients choose public hospitals because they cannot afford treatment in private hospitals but even here they pay for some drugs, tests and procedures, and this constitutes a burden that many cannot afford. The vast majority of Indians must pay for medical treatment from their own resources.

Patients in private hospitals are more able to afford treatment but catastrophic medical expenses can force them to sell assets, go into debt, or stop essential treatment. Various surveys have found that medical expenses are a major factor forcing many Indians below the poverty line5.In this situation, government moves to encourage clinical trials in India must be viewed with concern. Changes have been made in the law to permit international trials. Staff and infrastructure improvements and regulatory changes are meant to speed up processing of applications.

Public hospitals are being promoted as clinical trial sites. Monitoring systems are being set up to ensure high data quality and meet the requirements of drug regulatory authorities abroad. Training institutes are being encouraged to provide the humanpower to run clinical trials. The government has not expressed a stand on the manner in which the clinical research industry is growing in India. Clinical trials are conducted by contract research organizations (CROs) which are developing the infrastructure for trials by making inroads into small towns, identifying trial sites in small private hospitals and developing databases of potential trial participants.

Medical professionals are given substantial incentives to recruit their own patients into clinical trials. This situation creates a major conflict of interest that threatens the well-being of patients. India is viewed as a favoured global site for international clinical trials of drugs. According to the Drugs Controller General of India (DCGI), India will be a preferred site for clinical trials because, in addition to its medical infrastructure and trained, English speaking humanpower,

it has a “large, diverse and treatment-naïve [untreated] population with six out of the seven genetic varieties of the human race”; a pool of patients with both acute and chronic diseases, an increase in the number of patients with lifestyle disorders and the highest recruitment rates for such trials internationally6. The Indian government has seized upon this opportunity and is taking steps to change the regulatory climate here to accommodate the needs of international clinical trials.

Regulation of clinical trials

Clinical trials in India are regulated by Schedule Y of the Drugs and Cosmetics Rules. The Rules are enforced by the office of the DCGI who is also responsible for monitoring all clinical trials submitted to that office for approval. For new drugs being developed in India clinical trials have to be conducted in India from phase 1.

For marketing approval of drugs already approved in other countries, a phase 3 clinical trial is required on about 100 patients in three or more centres, in order to establish the drug's impact on the Indian ethnic population. An application for a new indication of an already approved drug is treated as an application for a new drug's approval.

New formulations of approved drugs may be subjected to bioequivalence studies. Till January 2005, clinical trials of new drugs being developed outside India were permitted only with a "phase lag": a phase 2 trial could be conducted in India only after phase 3 trials were completed elsewhere.

Phase 1 trials of foreign drugs were not permitted, except for drugs of special relevance to India. This clause enabled, for example, phase 1 trials of HIV vaccines in India. In fact, international multicentre trials have been conducted in India since the mid-1990s9.

Phase 2 and phase 3 trials of drugs discovered abroad may now be conducted in India in the same phase and at the same time as they are conducted in other parts of the world. The trial sponsor must obtain approval from the DCGI before starting a trial. For this approval, the sponsor must submit data from pharmacokinetic and animal studies and previous phase trials; information on the regulatory status of the drug in other countries, the trial protocol, investigator's brochures and informed consent documents. Trials cannot be started without clearance from the local ethics review committee (EC) at each site.

Phase II trials evaluate the effectiveness and safety of a drug on patients. Phase III trials are conducted on larger numbers of people to confirm the evidence from earlier phase trials towards obtaining marketing approval of the drug.

Phase IV trials are conducted after a drug obtains marketing approval. They are conducted for various purposes including monitoring for drug interactions and testing for new uses of the drug.

Government steps to promote clinical trials

At a meeting of the Institute of Clinical Research [India] (ICRI) in Mumbai, Surinder Singh, Drugs Controller General of India, described a number of other steps that the government plans to undertake towards encouraging international clinical trials in India16. In addition to changes in the law (that have already taken effect), single window clearance for applications is planned in order to reduce the approval procedure to between two and six weeks.

A two-tier approval process is already in place. Category A protocols consist of protocols from the US, United Kingdom (UK), EU and Japan. Category A trials will get fast track approval of six to eight weeks. Category B trials from other countries will get approval in eight to 12 weeks. The government will grant a license to import supplies within two weeks of the application being made. The DCGI has also promised that local EC review will be completed in six to eight weeks. By 2009, he said, timelines will be in harmony with international clinical trials. The DCGI announced plans to recruit subject experts and has also got approval for 60 new drug inspectors. 20 of these inspectors will be responsible exclusively for auditing clinical trials.

Trends in international clinical research in India

International clinical trials have been conducted in India starting in the mid 1990s though it was only in 2005 that regulations were changed to routinely enable concurrent phase trials. The DCGI has stated that there are 582 (registered) clinical trials being conducted in India, of which 72 per cent are conducted by the pharmaceutical industry17. (A search in October 2008 of www.clinicaltrials.gov for trials with a site in India lists 789 studies, planned, recruiting terminated and completed.)

Contract research organizations

Drug companies conduct clinical trials through contract research organizations (CROs), commercial entitites whose job it is to get the research done and to meet regulatory requirements. Since the early 2000s, there seems to have been a sharp rise in the number of contract research organisations functioning in India; the DCGI has stated that the estimated number of contract research organisations in India registered with the USFDA has gone from 60 to 150. CROs may handle some or all aspects of a sponsor's project including: regulatory approvals for trials, identifying recruiting sites and investigators, monitoring sites, data entry and management, submitting data for marketing approval and drafting study reports for submission to journals. These activities may also be split up and handled by different organizations. Some organizations focus exclusively on providing data management and statistical analysis. Trial sites that do not have institutional review boards may approach "stand alone" ethics committees not affiliated to any institution. Site maintenance organizations (SMOs) are focused exclusively on recruiting patients and coordinating the work of investigators conducting clinical trials18.

Why do people participate in clinical trials?

A CRO-conducted survey of the informed consent process in clinical trials provides some interesting information on the patient recruitment procedure and the quality of informed consent in clinical trials in India20. This survey was of patients participating in trials run by the 17 Surinder Singh, Drugs Controller General of India, at a conference of the Institute of Clinical Research (India), Mumbai, October 10-11, 2008.

They may also believe that refusal to follow the doctor's advice to enter a trial would affecttheir access to care. When the trial's principal investigator is also the person's primary physician, there is scope for a direct conflict of interest, especially if physicians are paid recruitment fees to recruit their patients into trials. The survey's findings on why people entered a clinical trial were enlightening:

- 15 per cent stated that they entered the trial because they were looking for a cure.
- 13 per cent were looking for "observed benefits".
- 15 per cent were looking for a better treatment.
- 16 per cent were looking for higher quality care.
- 10 per cent were looking for free medication and medical care.
- 15 per cent said the doctor advised them to enter the trial.
- 5 per cent said they entered the trial to receive money for participation.
- 11 per cent said they entered the trial to help advance scientific knowledge.

Some of the categories – such as "observed benefits" – are not clearly described. However, it is a matter of concern that 26 per cent of participants stated that they entered the trial to obtain free care or higher quality care. It is quite possible that such patients overlook risks to participate in trials. Another 15 per cent stated that they were following their doctor's advice – a possible concern if their doctor received fees to recruit them into the trial. The five per cent who entered the trial to receive money for participation are very likely to have overlooked the risks of participation.

According to the ICMR's guidelines, "… payments should not be so large or the medical services so extensive as to make prospective participants consent readily to enroll in research against their better judgment, which would then be treated as undue inducement." However, patients in bioequivalence trials (used to check that generic versions of approved drugs or for new formulations of approved drugs work as well as the approved drug) may have paid up to Rs 20,000 to participate in the trial.

Incentives for clinical trial investigators

When the government declared its plans to use government hospitals as clinical trial sites21, government institutions were already the sites for many clinical trials. Public hospitals are resource-starved (the per capita expenditure on health was $100 in

2005, of which less than 20 per cent was by the government22. In 2002, public expenditure on health was less than one per cent of the Gross Domestic Product23 and this percentage has not changed since then). Patients at public hospitals are often forced to go to private centers and pay for basic tests, drugs and supplies. Government doctors running trial sites do not officially receive fees for recruiting patients into clinical trials. A CRO with a trial site in a government institution will pay about 15 per cent of the budgeted expenses for that site directly to the institution.

The hospital department running a trial site gains some equipment and the salaries of junior/additional investigators are paid by the trial sponsor for the duration of the trial. Administrators and senior staff at government hospitals may view clinical trials as helping the work of an under-resourced hospital. Principal investigators also get invited to all-expenses paid conferences abroad. For government doctors, such trips may be enough incentive to conduct trials, even without recruitment fees. The incentives to investigators in private hospitals are more upfront; the investigator is paid according to the number of patients recruited (additional benefits include all-expenses paid trips abroad to attend conferences).

Appendix I

Contact and correspondence with investigators and institutions Contact with trial investigators

Shona Nag and Dinesh Doval were interviewed at their offices about the lapatinib trial. The third Indian investigator in the lapatinib trial could not be contacted. In the psychiatric drug trials, efforts were made to contact all the researchers in the three trials. The director of the National Institute for Mental Health and Neurosciences, one of the sites for the risperidone study was sent an e-mail asking for an interview. Face to face interviews were conducted with Jitendra Trivedi and Sumant Khanna.

A second interview with Dr Khanna was conducted on the telephone. Telephone interviews were conducted with Kurien Kuruvilla, R Sathianathan, V Debsikdar, and Prasad Rao. Podila Sharma and G K Vankar were sent a list of questions by e-mail. Dr Sharma acknowledged the e-mail. Shiv Gautam was contacted but could not be interviewed. R Palaniappan, J Nagpal and Nagesh Pai were not contactable. Dr Pai has reportedly migrated to Australia.

The following were sent an e-mail with the quoted statements, informing them that they were being quoted: Shona Nag, Dinesh Doval, Prasad Rao, Jitendra Trivedi, Sumant Khanna, R Sathianathan and V Debsikdar. Dr Debsikdar's e-mail obtained from his residence bounced back. Dr Kuruvilla was phoned for his e-mail address but did not give it on the phone and then refused to answer phone calls. Dr Nag, Dr Doval, Dr Khanna and Dr Trivedi gave their consent to their statements quoted in this report.

Appendix II

Contact and correspondence with the companies

During the shortlisting of trials, efforts were made to obtain an interview from the companiesconducting the trials. Two of the five companies (Eli Lilly, manufacturing exenatide, and Nycomed Pharma, manufacturing ciclesonide) responded stating that they would not provide any information. After the interviews with investigators in the four trials, efforts were made to contact a representative in the three companies, GlaxoSmithKline, Johnson & Johnson and AstraZeneca. Following this second round of telephonic contact, e-mails were sent to the the medical director of GlaxoSmithKline, Mumbai, the director (corporate communications), Johnson & Johnson, Mumbai and the director (corporate communications), Astra Zeneca, Bangalore. These letters were also delivered by courier.

The letters asked for details on the trials including the number of patients recruited at each site, economic background of patients and the information given to patients. A copy of the informed consent form, regulatory approval and details of the local ethics committee were also sought. Efforts to speak to the the director (corporate communications), Astra Zeneca, were fruitless and the company did not respond to were did not respond to e-mails sent to the e-mail company address or to Sheshendra Bhadauria, the director, corporate communications, whose name and e-mail address were obtained from the Bangalore head office.

Appendix III

Summary of the process identifying four drug trials for investigation

In the first stage of this work, various searches were conducted of the database www.clinicaltrials.gov using the keywords India, placebo control, mania, schizophrenia and depression, to identify ongoing trials with India sites whose trial design was likely to be of concern. This was not meant to provide an objective list, or a list that allowed for generalisability, as the objective of the study was only to document types of unethical research practices. After a discussion with Wemos and SOMO, it was decided that while a search for ongoing trials would be important, the objective of highlighting concerns in drugs approved for the EU would best be served by looking at completed trials that might have been used for approval by the European Medicines Agency (EMEA). The rest of the work was based on a shortlist sent by SOMO of trials with at least one site in India, and related to drugs that had been approved in the EU after 2004.

The trials were: four placebo-controlled phase 3 trials of quetiapine, a psychiatric drug marketed by Astra Zeneca;

Three phase 2 trials of lapatinib, a drug for breast cancer marketed by Glaxo Smithkline;

three phase 3 trials of ciclesonide, an inhaled steroid for asthma marketed by Nycomed Pharma/ Altana Pharma; one phase 3 trial of pregabalin for neuropathic pain marketed by Pfizer,one phase 3 trial of exenatide, an injectable drug for diabetes marketed by Eli Lilly,

and one phase 3 trial of amlopidine/atovorstatin, a combination drug for hypertension andhigh cholesterol marketed by Eli Lilly. In the first stage, available information was assembled about the trials: journal publications and other results obtained through www.ClinicalTrialResults.org, the company sites, and google searches of the trial titles.

The India offices of the companies were contacted by phone and e-mail, The representative of each company was informed that that we (Sandhya Srinivasan and Sachin Nikarge) were researchers with the Centre for Studies in Ethics and Rights and were interested in learning more about a trial of a drug manufactured by the company. The details sought were: the sites where the trial was conducted; the start and end dates of the trial; contact details of the institutions; the name of the CRO if one was involved; the names and contact details of the principal investigator, and membership and contact details of the ethics committee that reviewed the trial protocol. The representative of Eli Lilly (exenatide) replied on the telephone, refusing to provide details. The representative of Nycomed Pharma (ciclesonide) asked for an e-mail to be sent to the head office in Germany. Dr Christian Biberger, Director Clinical Trial Management Astra Zeneca, Eli Lilly, Pfizer, Altana Pharma and Glaxo Smith Kline.he letter delivered by courier.

UNETHICAL TRIALS IN INDIA

This briefing paper provides an overview of known examples of unethical clinical trials. It was prepared by SOMO, in collaboration with Wemos, and is based on secondary sources. Although the focus is on developing countries, it also includes a few cases from the US and Europe. By providing such an overview, the paper aims to illustrate problems in the ethical conduct of clinical trials. It does not provide an analysis of clinical trials in general or of the scale of ethical violations. Indeed, the scale of the problem is unknown, because it cannot be estimated how many unethical clinical trials escape public attention and therefore remain unnoticed.

There are some indications that underlying structural problems exist, though, as in several of the trials described in this paper, the operations of pharmaceutical research companies were not adequately controlled or authorities seemed unwilling to address unethical drug testing even after it caught media attention.

This overview is limited to clinical trials involving drugs and vaccines, as such recent controversies about trials of the Dutch company Occam in India involving stents, or circumcision trials or circumcision trials in Africa, have been excluded. Furthermore, the focus is on ethical issues related to the design and conduct of trials. Conflicts about intellectual property or illegal exports of blood samples are not described. For each trial, selected information sources are provided. Most sources are publicly accessible websites, but some require a subscription. The first version of this briefing was published in November 2006.

The present version, which is the second update, does not include new cases but adds more recent developments on several trials, takes into account feedback from three companies, and has updated sources. For each trial, selected information sources are provided. Most sources are publicly accessible websites, but some require a subscription. The first version of this briefing was published in November 2006.

Ethical norms

The case descriptions also refer to norms in widely accepted international codes that have (probably) been violated. The most cited reference is the Declaration of Helsinki (DoH) of the World Medical Association (WMA). European regulations specify that the trials providing the underlying data for marketing applications of new drugs need to comply with the Declaration of Helsinki. The World Health Organization (WHO) Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products also endorses the DoH as the accepted basis for clinical trial ethics. Some important paragraphs from the declaration are briefly summarized below.

As placebo-controlled clinical trials (DoH §29) are currently a standard practice rather than an exception (for phase III studies), this overview does not include trials that could be considered controversial solely because drugs were tested against placebos where proven alternatives already existed. Some examples of trials with controversial use of placebos can be found in: Furthermore, despite recent initiatives to increase transparency about drug trials, the design of most studies is still not publicly available (DoH §16). Therefore this principle was also not used as a selection criterion for the overview of unethical clinical trials in this

General observations

Even though the overview below is necessarily incomplete and biased towards unethical trials that have caught some publicity, some general observations can still be made. Firstly, unethical trials have occurred around the world, in both developed and developing countries. In some cases, the trials had not been approved by an ethical review committee or institutional review board, or approval had be given for an unethical trial design. Hence there appear to be flaws, and sometimes rather serious ones, in the regulatory systems of various countries.

Secondly, the research organizations involved range from relatively unknown local companies to leading multinational corporations. This might be surprising, given that large multinational corporations usually have clear public commitments to high ethical standards in clinical trials.

Thirdly, some of the unethical trials are of a recent date, some were even being carried out in 2005 or later. Although it is sometimes argued that instances of unethical clinical trials are isolated and outdated, this is not always true. Note that some older cases have been included in the overview as well, mainly because the developments following these trials are still going on.

And finally, the nature of ethical concerns appears to be rather diverse and relates to all paragraphs of the DoH summarized above.

The lack of voluntary, informed participation and adequately informed consent are probably the most common problems. Cases of trials that did not undergo adequate ethical review or failed to report serious adverse events indicate flaws in the regulation of clinical trials. Tests with experimental drugs of which the safety for testing in humans had not yet been fully established may be among the most alarming examples.

Examples of unethical trials

Letrozole trials in India

Letrozole trials in India Drugs:	**letrozole**
Treatment	Inducing ovulation
Sponsors	Sun Pharmaceuticals
Period	2003
Location	India

Unethical aspects

Letrozole, which belongs to the group of aromatase inhibitors, was tested by Sun Pharmaceuticals to induce ovulation. The drug has been approved globally for the treatment of breast cancer in post-menopausal women, but it is not approved for any other use in any country. without their knowledge or consent to take part in clinical trials conducted at nine or more centres across.

Outcome

A complaint on the letrozole case was filed in the Supreme Court by the Delhi-based NGO Social Jurist. Novartis, who was not involved with the study but markets letrozole under the brand name Femara, sent a clarification letter to all infertility experts in India to remind them of the approved indication india.

Streptokinase trials in India

Drugs:	streptokinase (Streptokinnese / Streptase) and insulin
Treatme	Clot-busting drug used in heart attacks, diabetes
Sponsors	Shanta Biotechnics (streptokinase), Biocon (insulin)
Period:	2003
Location:	Hyderabad, India

Unethical aspects

The companies had openly conducted illegal phase III clinical trials of new drugs on unaware patients and had conducted improper clinical trials without permission from the Genetic Engineering Approval Committee (GEAC). Eight patients died. Shanta Biotechnics denied the allegations.

Violated norms

The trial protocol was not reviewed by an ethical review committee. Subjects were not informed they were participating in a trial. Informed consent was not obtained.

Risperidone trials in India

Drugs:	risperidone (Risperdal)
Treatment:	Treatment of acute mania
Sponsors:	Johnson & Johnson
Period:	Unclear, probably 2003
Location:	Gujarat, India

Unethical aspects

During a trial for the treatment of acute mania, psychiatric patients were taken off their existing medication and told that it was discontinued and no longer available. They subsequently received risperidone or a placebo. This was controversial because the patients receiving a placebo could suffer unnecessary harm by being taken off their medication. One patient explained that he signed a form because the doctor required it, but had no idea that he was participating in a clinical trial.

Violated norms

Not all subjects were informed they were participating in a trial. Informed consent was not properly obtained from all participants.

The use of a placebo was controversial because it was unnecessarily dangerous. It was not explained to all patients that the provided medical care was linked to a research.

Outcome

Johnson & Johnson denies the allegations and stated that consent had been obtained from every patient. It defended that placebo-controlled trial expose less patients to a potentially ineffective treatment. However, this does not explain while patients have to discontinue a proven existing treatment

Cilansetron trials in India

Drugs	cilansetron (Calmactin)
Treatmt	Treatment for diarrhoea from Irritable Bowel Syndrome (IBS)
Sponsor	Solvay Pharmaceuticals
Period	Unclear, probably around 2000
Locatio	India

Unethical aspects:

Phase III trials involving cilansetron, a new molecule of Solvay Pharmaceuticals, were cleared by the Drugs Controller General of India (DCGI) even though only Phase II trials had been conducted abroad. At the time, trials of foreign drugs were permitted in India only at one step below the phase completed abroad.

Violated norms:

Before 2005, the Schedule Y of the Indian Drug and Cosmetic Act prohibited clinical trials in India of drugs developed outside the country before Phase II trials were completed abroad. Phase III trials of such drugs were only allowed if the drug had already been fully tested elsewhere.

Zoniporide trials in India

Drugs	zoniporide
Treatment	Perioperative cardiac events
Sponsors	Pfizer
Period	Unclear, probably around 2000
Location	India

Unethical aspects:

The Drugs Controller General of India (DCGI) approved Phase III trial of Pfizer's zoniporide while Phase II trials had not been completed in the USA and carcinogenic and reproductive studies on animals mandated by Indian law had not been completed.

Violated norms

Required animal experiments had not yet been completed. Before 2005, the Schedule Y of the Indian Drug and Cosmetic Act prohibited clinical trials in India of drugs developed outside the country before Phase II trials were completed abroad. Phase III trials of such drugs were only allowed if the drug had already been fully tested elsewhere.

Cilostazol trials in India

Unethical aspects:

Drug trials were cleared by the Drugs Controller General of India (DCGI) based on incomplete, inadequate information on adverse effects. Common serious side-effects such as angina and myocardial infarction were not mentioned.

NDGA trials in India

Drugs	nordihydroguaiaretic acid (NDGA)
Treatment	Treatment for oral cancer
Sponsors	Johns Hopkins Hospital (US)
Research organization	Regional Cancer treatment Center (RCC)
Period	1999 – 2000
Location	Trivandrum, India

Unethical aspects:

The drug was tried on 26 cancer patients before its safety was established in animal tests. The patients were not informed that they were taking part in an experiment or that they were being denied an established treatment and two of them died. Subsequently, a 60-year-old woman was again included for a trial in which the RCC provided five doses of the experimental drug. The woman's condition turned critical before the fifth dose but she survived.

Violated norms

Required animal experiments had not yet been completed. Subjects were not informed they were participating in a trial. Informed consent was not obtained.

Ragaglitazar trials in India

Drugs	ragaglitazar
Treatment	Diabetes treatment
Sponsors	Novo Nordisk
Period	2002
Location	32 countries, including India

Unethical aspects:

Indian scientists questioned the ethics of the phase III clinical trials of the drug before it was fully tested on animals. The trials were conducted in 32 countries, inlcuding EU countries and the US, and involved 2,500 people. Novo Nordisk stated that prior approval had been obtained in each country. The trials were suspended by the company after it discovered a mouse (and several rats) treated with the drug had developed urinary bladder tumours. In India, 130 people from eight centres participated in the trials. Half of them received the experimental drug.

Violated norms

It was disputed whether required animal experiments had been completed. Under Indian Council of Medical Research (ICMR) regulations, the results of toxicity studies on drugs for chronic diseases had to be available before phase III clinical trials begin. In the EU and the US, this is not required.

CONCLUSION

The level of concern about the impact of the CTD on clinical research activities is intense and widespread overall stakeholder groups. Opinions and quantitative survey results draw a picture of increased bureaucracy and costs, reduction of important research without creating benefits for patients. However, concrete, comprehensive figures about the clinical trial activities are only available from competent authorities. Figures on the CTD's impact on organisation, staffing, costs and processes of the different stakeholders are missing.

Based

These trials violated the the Indian Council of Medical Research's Ethical guidelines for biomedical research on human subjects and the World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. The trial designs do not seem to have violated regulations for the conduct of clinical research in India. The existing regulatory apparatus therefore permits unethical trials of no benefit to Indians. Clearly, trials are being conducted in India that could not be conducted in developed countries, taking advantage of people's lack of access to affordable, good quality care.

The benefits of research do not reach the community as drugs found effective following these trials may not be affordable to the community in which they were tested. Such practices are in violation of the Declaration of Helsinki as well as the general principles laid down in the Indian Council of Medical Research's ethical guidelines for biomedical research.

The infrastructure for regulation, ethics review and monitoring is insufficient. The government's priority seems to be ensuring that clinical research in India produces good quality data according to Good Clinical Practice standards. Ethical guidelines – including its own ethical guidelines – seem to be of secondary importance. The ethical concerns raised by these clinical trials; the weak regulatory apparatus to protect trial participants, government policy to encourage international clinical trials without taking active steps to put in place a system to protect participants from harm; people's desperation for affordable health care – all this will only worsen the harm being done to trial participants in India.tum since the discussions that were convened by the IOM

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