Clinical Trials VIS-À-VIS Ethics

Abstract

Medicine" doesn't have the benefit of being an exact science like mathematics and physics are. It does have some general principles but every patient is different and what is an effective treatment for 90% of the population, may not work for the other 10%. Thus, medicine is inherently an 'experimental branch'. Even the most widely accepted treatments need to be monitored and evaluated to see whether they are effective for specific patients, and, for patients in general. This is one of the functions of, MEDICAL RESEARCH.

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The recent reporting of controversial drug trials being conducted by doctors of the government medical college and private practitioners on 'mentally challenged' patients in Indore has caused uproar. It was alleged that for more than two years, from 2008 to 2010, trials were conducted flouting ethics guidelines. The Madhya Pradesh government levied a fine of Rs 5000 each on the doctors involved, and this was seen widely as being insufficient punishment. As details emerged, questions were raised about the role of independent or commercial (as compared to institutional) ethics committees, improper documentation of consent, as well as vulnerability of research participants.

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Keywords: Anatomy, Biochemistry, Cellular Biology, Immunology, Microbiology, Molecular Biology, Neuro Science, Pharmacology, Physiology, Efficacy, Pharmaceutical Company, Therapeutic Goods Administration, Infrastructure Improvements, Intoxication, Alzheimer's Disease, Whistle Blowing, Placebo Controlled Trials, Schizophrenia, Psychiatric Disorder.

Introduction

The Biomedical research can be sub-classified as basic/pre-clinical research and clinical research. Pre-clinical biomedical research is important for expanding the knowledge of basic biological mechanisms. Studies are commonly conducted in pre-clinical departments or institutions in fields such as anatomy, biochemistry, cellular biology, immunology, microbiology, molecular biology, neuroscience, pharmacology and physiology. Pre-clinical research can contribute to the discovery of new medical treatments. Clinical research ranges from clinical laboratory or investigational studies to testing of new clinical procedures, new clinical diagnostic tools and new medicinal products in humans. The most common method of clinical research for physicians is "CLINICAL TRIALS".

Before a new drug can be approved by government mandatedregulatory authorities, it must undergo extensive testing for safety and efficacy. The process begins with laboratory studies followed by testing on animals.Clinical trials are the mandatory bridge between pre-clinical discovery of new medicinal products and their general uses.

The foursteps, or phases, of clinical research on humans, are:

Phase One Research

Usually conducted on a relatively smallnumber of healthy volunteers, who are often paid for theirparticipation, is intended to determine what dosage of the drugis required to produce a response in the human body, how the body processes the drug, and whether the drug produces toxic or harmful effects.

Phase Two Research

Is conducted on a group of patients who have the disease that the drug is intended to treat. Its goals are to determine whether the drug has any beneficial effect on the disease and has any harmful side effects.

Phase Three Research

Is the clinical trial, in which the drug is administered to a large number of patients and is compared toanother drug,and/or to a placebo.

Where possible, such trials are 'double-blinded', i.e, neither research subjects nor their physicians know who is receiving which drug or placebo.

Phase Four Research

Takes place after the drug is licensed andmarketed. For the first few years, a new drug is monitored for sideeffects that did not show up in the earlier phases. Additionally,the pharmaceutical company is usually interested in how well the drug is being received by physicians who prescribe it andpatients who take it [1]

Each country has its own drug regulatory authority with its own regulations for approving clinical trial protocols and also for conducting clinical trials when testing and approving new medicines and other medicinal protocols.

Drug regulatory authorities come under different names in different countries. For instance, in the US the authority is the Food and Drug Administration, or FDA; in the European Union it is called the European Agency for the Evaluation of Medicinal Products (EMEA); and in Japan, the Ministry of Health, Labor and Welfare, or (MHLW). Other examples are Health Canada (Canada), the State Food and Drug Administration (SFDA, China), the Therapeutic Goods Administration (TGA, Australia), the DrugsController General of India (DCGI, India), the National Health Sanitary Surveillance Agency (ANVISA, Brazil), and the Federal Service on Surveillance in Healthcare and Social Development (Roszdravnadzor, Russia).

Responsibilities of the Regulatory Authority

1. Reviewing and approving clinical trial protocols.
2. Ensuring that clinical trials comply with national regulations of a country and international guidelines.

Such clinical trials can lead to various moral & ethical issues in terms of the physician, the researcher as well as the patient.Many problems arise in the day to day setup with regard to ethics in such trials. It is the duty of the authorities in concern with the trials to avoid and solve such issues.Multi-national pharmaceutical companies are moving their clinical trials business to India, giving a new urgency to clinical trials registry reform.

The question is: Why Indian people make themselves experimental objects even when they are aware that they will be threatening their lives by becoming the trial subjects? The answer is deep rooted in the scenario in the health care sector in India which is worth Rs.1,500 billion out of which only 15 %comes from government and over 80 % by the individuals using private services without insurance and 2/3rd of health care users bear 100 % of their health care expense. 70 % of these health care users are poor and thus an easy target for the drug companies. Patients in government & private hospitals are desperate for better quality and affordable care which is sometimes an added incentive if a person becomes trial subject. Medical expenses are so exorbitant that many Indians below the poverty line are forced to become trial object, sometimes, doctor also play a part in convincing their patients for the trials and since doctor-patient relationship in India unequal, patients do not question their doctors judgement and get influenced by the his advice. Many also believe that refusal to follow the doctors advice to enter a trial would affect their access to care.The Indian government has also shown quite an interest towards these companies and thus taken some initiatives for staff and infrastructure improvements & done regulatory changes so as to speed up processing of applications for the trials. 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 subjects to run clinical trials and single window clearance for applications is being planned in order to reduce the approval procedure to between two and six weeks and medical professionals are given substantial incentives to recruit their own patients into clinical trials. This creates a major conflict of interest that threatens the well-being of patients. Also, the government has no stand on the manner in which the clinical research industry is growing in India.

Research is often concerned with collecting data from people, this raises question about the way in which people who provide data should be treated by researchers & questions should be ethical in nature.[2]

Clinical trials in india are regulated by the revised schedule Y and the DGCI... an ethics committee sets up certain criteria to be followed during the trial.Such clinical trials can lead to various moral & ethical issues in terms of the physician, the researcher as well as the patient.

Many problems arise in the day to day setup with regard to ethics in such trials. It is the duty of the authorities in concern with the trials to avoid and solve such issues. Due to this, certain criteria & rules have been laid down to be followed in crinical trials[3].They are briefly enumerated as:

Investigator

The qualifications should be as prescribed by the medical council of india. He should sign and send all reports, analyses, results & interpretations to the sponsors as well as the ethics committee.its his duty to follow & let others follow all the protocols of the trial. An investigator is a person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team. A more formal definition of an investigator is "under whose immediate direction the test article is administered or dispensed to, or used involving, a participant, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team."

Responsibilities of the Investigator (Examples)

1. Protecting the rights and well-being of the participants.
2. Following GCP and other guidelines.
3. Having access to all necessary facilities.
4. Following the protocol.
5. Ensuring the clinical trial is reviewed by an EC.
6. Informing the EC of any adverse events.
7. Ensuring an ongoing informed consent process for the participants.

8. Protecting participants' identity.
9. Proper handling of all trial medications/supplies.
10. Reviewing and reporting adverse events during the trial[4]

Informed Consent

The research subject should havesufficient knowledge and comprehension of the elements of thetrial, the shortcomings, the outcome and consequences.An informed consent can be said to have been given based upon a clear appreciation and understanding of the facts, implications, and future consequences of an action. In order to give informed consent, the individual concerned must have adequate reasoning faculties and be in possession of all relevant facts at the time consent is given. Impairments to reasoning and judgment which may make it impossible for someone to give informed consent include such factors as basic intellectual or emotional immaturity, high levels of stress such as PTSD or as severe mental retardation, severe mental illness,intoxication, severe sleep deprivation, Alzheimer's disease, or being in a coma.Some acts can take place because of a lack of informed consent. In cases where an individual is considered unable to give informed consent, another person is generally authorized to give consent on his behalf, e.g., parents or legal guardians of a child (though in this circumstance the child may be required to provide informed assent and conservators for the mentally ill[5]

Confidentiality

As with patients in clinical care,research subjects have a right to privacy with regard to their personal health information.Privacy for research participants is a concept in research ethics which states that a person in human subject research has a right to privacy when participating in research.In both cases, the ideal outcome is that any participant can join the study and neither the researcher nor the study design nor the publication of the study results would ever identify any participant in the study.

People decide to participate in research for any number of different reasons, such as a personal interest, a desire to promote research which benefits their community, or for other reasons. Various guidelines for human subject research protect study participants who choose to participate in research, and the international consensus is that the rights of people who participate in studies are best protected when the study participant can trust that researchers will not connect the identities of study participants with their input into the study.

Honest Reporting of Results

There have been numerous recentaccounts of dishonest practices in the publication of research results. Problems include data fabrication, duplicate publication and 'gift' authorship. Such practices may benefit the researcher, at least until they are discovered, but they can cause great harm to patients, whomay be given incorrect treatments.The sponsor, investigator and institution have an ethical responsibility to make reasonable efforts to publicly disseminate the results of clinical research in a timely manner. However, it has to be accepted that negative research results are less often submitted and accepted for publication in international medical journals. The investigators must anyhow submit a final report of the trial to the EC for review and approval, providing details about major outcomes of the trial[6]

Whistle-Blowing

In order to prevent unethical research from occurring, or to expose it after the fact, anyone who has knowledge of such behaviour has an obligation to disclose this information to the appropriate authorities.

Compensation

In case of any harm or damage to participants, proper compensation & dues are given to the patient.these are given in accordance to the rules and regulations of the ethics committee.an indemnity arrangement is made to provide legal protection for the participants in the event of an unforeseen adverse circumstance arising during the course of a clinical trial. Indemnity is a form of contract to compensate an individual for loss or damage. To cover the costs that may be incurred as a result of providing indemnification, the indemnifier can obtain clinical trial insurance. It is important that clinical trial participants are insured to provide treatment for adverse events linked to participation in a clinical trial.Clinical trials insurance should cover the following liabilities:

1. Professional negligence in the course of conducting clinical trials.
2. Product liability, in case a product under investigation causes injury.
3. No-fault liability–intended to provide compensation to research participants, regardless of liability, in the event of their suffering a significant and enduring injury (including illness or disease) which, on the balance of probabilities, is attributable to their involvement in the clinical trial.

Right to withdraw

There is full right for participants to step back from taking part in the clinical trials in case if they don't want to participate.

Vulnerable Populations

The key issue of vulnerability is to assess the potential participants' mental capacityto give consent. This type of vulnerability occurs when participants have diminished mental capacity to give consent, such as adults with dementia or children. Others who have diminished capacity to provide consent are students, prisoners, women in certain cultures, and employees. We should note that pregnant women themselves are not vulnerable unless the trial occurs when the woman is in labor or delivery; the vulnerability is with the fetus.

The ICH-GCP Guidelines to be Followed

1. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
2. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
3. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

4. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
5. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.
6. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
7. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
8. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
9. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
10. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
11. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
12. Systems with procedures that assure the quality of every aspect of the trial should be implemented.7

Despite all the strict norms, regulations both international as well as national, various flaws and scandals in this regard have come up in our country in the recent times. DCGI had submitted in court in January 2013 that 475 human clinical trials for "new chemical entities not approved as drugs for human use anywhere in the world" were approved by the Indian drug regulator between January 2005 and 30 June 2012. Out of the 475 experimental drugs, 17 have been given approval for marketing, according to court records.During the period, 11,972 serious adverse events, excluding deaths, were reported, out of which 506 have been attributed to clinical trials. None of the victims has been compensated. A total of 57,303 subjects were enrolled in these clinical trials and 39,022 of them have completed the trials.The magnitude of the problem is now emerging with the government admitting thno laws were in place between 2005 and 2012 for new chemical entities and yet the government was approving trials so casually[8]

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To quote further examples, various trials done in india on some drugs have been enumerated and pointed out as serious flaws in clinical trials

Quetiapine

Risperidone

Lapitinib

Lapatinib, Glaxo Smith Kline

1. This Phase 2b trial of lapatinibmonotherapy for chemotherapy naïve patients with advanced HER2 positive breast cancer had three sites in India.
2. The majority of breast cancer patients in India cannot afford proper treatment. This trial required seriously ill patients who had not received treatment for their condition. Their economic vulnerability forces patients in India to take part in trials in order to get access to treatment and to disregard the potential risks that participating in clinical trials entails. By carrying out this clinical trial in India GlaxoSmithKline (GSK) took advantage of the vulnerable position of breast cancer patients.
3. The statement by a representative of GSK suggests that patients, who stopped responding to lapatinib, were not assured treatment once the trial was completed.
4. As a concurrent phase multi-country trial conducted before January 2005, the trial contravened an Indian government regulation that was in place when it was conducted. The company's statement does not indicate that the trial was permitted as an exception tothis regulation.
5. The approved drug is not affordable to the vast majority of Indians who could benefit from it.

Risperidone, Johnson & Johnson

1. This placebo-controlled trial of risperidone for acute mania was conducted in seven sites in India.
2. It used a trial design that is required by United States (US) regulatory authorities but is viewed by many – including the lead investigator – as methodologically unnecessary.
3. Patients in the risperidone trial were recruited from both government and private hospitals. More than two thirds of patients were recruited from government hospitals where the most severely ill patients are found.
4. Patients in this trial from government hospitals may have viewed trial participation as a way to get improved care as clinical trials require monitoring for efficacy and safety. Patients in this trial from private hospitals may have viewed trial participation as a way to get free care.
5. The patients in this trial were much more severely ill than similar trials of risperidone conducted in the US and other developed countries. The severity of their illness could have affected their ability to consent.
6. Patients in this trial were suffering from an acute attack of a psychiatric condition that would have caused them much distress. They were harmed because they were taken off all treatment before

they were put on either the active drug or a placebo. Those on the placebo were also harmed because they were deprived of an effective treatment.

Quetiapine fumurate Extended Release, Astra Zeneca

1. The two placebo-controlled trials of quetiapine were conducted on patients with schizophrenia. An immediate release formulation of the drug had already been approved and these trials were of an extended release version of the drug.
2. The trials examined the drug's impact on patients with acute schizophrenia and for long term maintenance therapy in schizophrenia.
3. The trial design in these trials was not necessary. Placebo-controlled trials are not required to establish the efficacy of a new formulation of an approved drug. Nor are they required by regulatory authorities in India.
4. Patients in the quetiapine trials in India were recruited from both government and private hospitals. Patients in this trial from government hospitals may have viewed trial participation as a way to get improved care as clinical trials require monitoring for efficacy and safety. Patients in this trial from private hospitals may have viewed trial participation as a way to get free care.
5. Schizophrenia is a serious psychiatric disorder and withholding effective treatment causes patients harm. Patients in the trial of quetiapine for acute schizophrenia were harmed when they were taken off all treatment before being put on either the active drug or a placebo. Patients on placebo – in both trials – were also harmed because they were deprived of an effective treatment until they suffered a relapse.
6. A patient in one of the quetiapine trials committed suicide after 173 days of being on placebo. The authors of the journal article reporting on this trial have stated that this suicide is "not considered treatment related". Suicide is a known risk for patients with schizophrenia. The investigators do not explain how they concluded that the suicide was unrelated to the treatment. The possibility cannot be ruled out that the patient committed suicide because s/he was deprived of effective treatment.[10]

Hence, despite all safety measures or regulations, there is failure on part of authorities to regulate clinical trials india& on ignorance on part of the participants taking part in the trials.It can lead to social, mental, economic, health related backdrop in india.Such problems need to be addressed in the present world,also endeavours need to be made for proper enforcement of RESEARCH ETHICS.....

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