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Systematic review on: Clinical research & clinical trial

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Abstract
Medical science owes much to the development of the clinical research method known as the clinical trial (CT), which plays a key role in modern clinical research and is considered to provide the best level of evidence in evidence-based medicine. Carefully conducted clinical trials are fastest and safest way to find treatment that work in people and way to improve health. Clinical trials aim to measure therapeutic effectiveness and constitute an important and highly specialized form of biological assay. This paper is intended for people who need to understand Clinical research & clinical trial terminology and is directed in particular towards Health care professionals, nurses and pharmacists reading clinical trial reports. The coverage of material is meant to assist with understanding what clinical trials involve – it covers the majority of terms that are likely to be encountered and is a phases of clinical trials. A variety of medical, ethical terms & definitions are included. It is hoped that this paper will assist readers who understand little or nothing of terms relating to clinical trials to appreciate their essential meanings. References are provided for readers to follow-up the complete details of all the terms used.

Keywords: Institutional review board (IRB), Drug Controller General of India (DCGI), Clinical research, Investigational New Drug (IND)

Introduction

Clinical research is a branch of biomedical science that determines the safety and effectiveness of medications, devices, diagnostic products and treatment regimens intended for human use. These may be used for prevention, treatment, diagnosis or for relieving symptoms of a disease. Clinical Research is different from clinical practice. In clinical practice one uses established treatments i.e. it is after the clinical trials or manufactured drugs is used for the treatments of diseases for the patients, while in clinical research evidence is collected to establish a treatment.

The term clinical research refers to the entire bibliography of a drug Once the promising candidate or the molecule is identified in the lab, it is subjected to pre-clinical studies or animal studies where different aspects of the test article (including its safety toxicity if applicable and efficacy, if possible at this early stage) are studied. [1]

The data obtained from the pre-clinical studies or other supporting evidence, case studies of label use, etc. are submitted in support of an Investigational New Drug (IND) application to the FDA for review prior to conducting studies that involve even one human and a test article if the results are intended to be submitted to or held for inspection by the FDA at any time in the future.

In addition clinical research may require Institutional Review Board (IRB) or Research Ethics Board (REB) and possibly Other institutional Committee reviews, Privacy Board, Conflict of Interest Committee, Radiation Safety Committee, Radioactive Drug Research Committee, etc. approval whether or not the research requires prior submission to the FDA. Clinical research review criteria will depend on which federal regulations the research is subject to (e.g., (Department of Health and Human Services (DHHS) if federally funded, FDA as already discussed) and will depend on which regulations the institutions subscribe to, in addition to any more stringent criteria added by the institution possibly in response to state or local laws/policies or accreditation entity recommendations.

Clinical research is often conducted at academic medical centers and affiliated research study sites. These centers and sites provide the prestige of the academic institution as well as access to larger metropolitan areas, providing a larger pool of medical participants.

In order to conduct a clinical trial in India, permission is primarily needed from regulatory authority of India, ie, Drugs Controller General of India (DCGI), and also from institutes where the trial will be conducted.

The DCGI is a body that falls under the Health Ministry and is responsible for regulatory approvals of clinical trials in India. Its functions include approval of trial, importing the drug for trial and sending biological overseas for testing. The DCGI follows Schedule Y of Drugs and Cosmetic Act, which was laid down in 1945, and was recently amended in January 2005. Schedule Y defines the requirements and guidelines for import and/or manufacture of new drugs for sale or for clinical trials. These include details of the application process and components of the application for permission to conduct clinical trials, and the responsibilities of the sponsor, investigators, and the Independent Ethics Committee (IEC). The change is promising and is supportive to the industry for clinical trials. Earlier, foreign drug trials could be conducted only in one phase below the highest phase of testing abroad. Parallel global clinical trials are now being conducted in India as well, ie, permission is granted for concomitant phase II and III trials [2, 3].

As per the rules, the applicant has to submit details such as chemical and pharmaceutical data; generic & chemical name; dosage form; composition; animal pharmacology & toxicity data; animal toxicology and clinical data; as well as phase I, II, III & IV data to the DCGI. The protocol of the clinical trial with a consent form is also submitted. The authority also needs to know about the regulatory status of the drug in other

countries, including names of countries where the drug is approved, and international package insert or the place where Investigational New Drug (IND) application is filed. Applicants have to report any Suspected or Unexpected Serious Adverse Reaction (SUSAR) from participating countries, if any. Further, it is necessary to submit an affidavit from the sponsor stating that the study has not been discontinued in any country. In case of discontinuation, reasons for the same must be communicated to the DCGI. The process of approval can take up to 10-12 weeks as compared to an average of 30 days in the US Food and Drug Administration (USFDA) and 60-90 days in Europe.

After the initial approval, it is mandatory to send safety reports in real-time and one annual report with all details of the study in India. After the study is complete, a detailed report must be submitted to the DCGI. The DCGI also undertakes inspections to ensure that trials are conducted as per protocol, ethics and the laid guidelines.

There are three primary groups involved in the conduct of clinical trials: sponsors, clinical investigators and IRBs.

Sponsors

An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.

Clinical investigators

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and nonscientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Institutional Ethics Committee (IEC)/Institutional Review Board (IRB) [4-7]

The health care team involved in research is ethically bound to respect human life and peoples' autonomy. Good research practice demands that researchers must respect the rights of their subjects, listen to and share information with them, and treat them courteously and caringly.

Ethics refers to moral principles governing human character and conduct. The principles of medical ethics, introduced by Beauchamp and Childress in 1979, are as much relevant to the medical research as they are to healthcare.

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 nonintervention studies (observational studies or those using already collected data). In the U.S., this body is called the Institutional Review Board (IRB).

IRB it is an Institution Review Board (IRB) is a committee of health care professionals and community members, who review, approve, and monitor clinical trials to make sure potential risks are as low as possible and that the clinical trial follows ethical and legal codes for medical practice. The regulatory responsibilities of IRBs are found primarily in 21 CFR 56.

Every clinical trial in the United States is required by the Food and Drug Administration (FDA) to be approved and monitored by an Institutional Review Board (IRB). This is an independent committee of medical professionals who review protocols that are proposed by researchers in their institution. Their job is to ensure that the study is scientifically well designed and to protect the rights and safety of the participants. Many research protocols are also reviewed by Data Monitoring Committees. This is a committee of medical professionals who are independent of the researchers and who review the information that is being collected by the clinical trial while the trial is still in process. If there is evidence that the new medicine or treatment is unsafe or of no benefit, this committee can stop the study.

Most RBs 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 Rib'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.

The IRB approval process can be conducted in parallel with the DCGI review. The provisions facilitate the process of having study protocols in place and quickly initiating trials. In order to comply with all applicable regulatory requirements and guidelines, each IRB must have the following records:

1. Written Standard Operating Procedures (SOP) or charter
2. Constitution and composition of the IRB
3. Curriculum vitae of all IRB members
4. Copies of all trial documents received for review
5. All correspondence between IRB and investigator
6. Agenda and minutes of all IRB meetings
7. Final report of the study

After granting the approval for conducting clinical trial(s), it is the responsibility of IRB to have a review of the trial in progress. This includes but is not limited to:

1. Review of safety reports (all serious adverse events and adverse drug reactions happening at the trial sites)
2. Review and approval of amendment(s) in protocol or informed consent document
3. Review of significant deviations or violations (if any)

The frequency of these reviews may vary from one institute to another, as specified in the respective IRB charters or SOPs, but is usually once in 4-8 weeks. The usual time for approval by the Ethics Commitee (EC) is 6-8 weeks.

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 Harmonization 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 declaration of Helsinki of the World Medical Association (1964) codifies recommendation for guidance of doctors in clinical research.

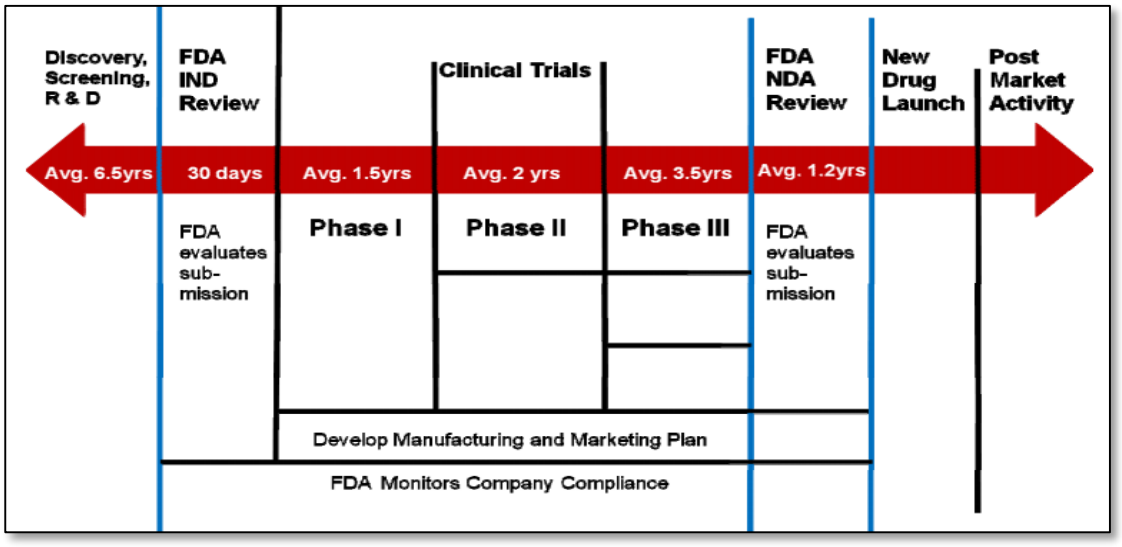

Fig 1: Process of drug development.

Pre-clinical studies

Before pharmaceutical companies start clinical trials on a drug, they conduct extensive pre-clinical studies. These 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, & pharmacokinetic information. Such tests assist pharmaceutical companies to decide whether a drug candidate has scientific merit for further development as an investigational new drug. If preclinical studies show that the therapy is safe and effective, clinical trials are started.

Such experiments helps the pharmaceutical companies to decide whether the drug have scientific merit or not. In addition, decision on whether it has been required for further development as an investigational new drug.

Clinical studies/Clinical trials [8-13]

- Clinical trials may be defined as the process designed to determine the safety and efficacy of a particular drug or device on humans. Or,
- A clinical trial is a research study that tests a new medical treatment or a new way of using an existing treatment to see if it will be a better way to prevent and screen for diagnose or treat a disease. Or,
- "Scientifically controlled studies of the safety and effectiveness of a therapeutic agent using consenting human subjects", Or,
- A clinical trial is a research project that compares two or more treatments in patients with a particular condition or at risk of a condition to help generate high quality evidence about which is the more effective treatment or preventative strategy.

A clinical trial is sometimes called a clinical study. A clinical trial:

1. Is a research study that tests how well an intervention works in a group of people
2. Tests for new methods of screening, prevention, diagnosis, or therapy
3. Is conducted in phases

Why clinical trials needed

- Clinical trials test how investigational drug work in people
- Approaches can be medical, behavioural , or management
- Study answers scientific questions
- Study helps prevent screen manage and disease

Classification of the trials/ Phases of Clinical trials [14-17]

Clinical trials must follow certain procedures, to satisfy regulation requirements for development of a new drug in humans. The US Food and Drug Administration (FDA) first described the four `phases' of clinical trials (Fig. 2); this terminology is now widely accepted throughout the pharmaceutical industry. Under this system, a new drug or intervention begins testing in phase me trials and then proceeds to phase II and III trials in a sequential manner that ends with the intervention being established as the new standard or in its licensing.

After licensing, a phase IV trial may be undertaken to explore the long-term morbidity and effects that would be too uncommon to be detected in previous studies.

Classification of the trial may reflect how the researchers behave (observational versus interventional clinical trials), by their purpose (prevention, screening, diagnostic, treatment, quality of life, or expanded access clinical trials), or whether the trial design allows changes based on data accumulated during the trial (fixed versus adaptive clinical trials).

	Objective	Typical No. of patients
Phase I	♦ First investigation of a new drug in humans (often called `first in man' studies) ♦ To investigate the pharmacokinetics and the pharmacological effects of a drug, including dose-response and side effects	10 to 30, usually healthy volunteers
Phase II	♦ Provides preliminary efficacy and safety data	Fewer than 100
Phase III	♦ To compare new treatment to the standard therapy or a control or placebo (if no standard treatment exists) ♦ Phase IIIb studies investigate new indications for already licensed drugs	Hundreds or thousands
Phase IV	♦ Long-term surveillance of patients to identify morbidity and late effects (post-marketing study)	Many thousands

Fig. 2 Phases of clinical trials.

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. 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 sub therapeutic 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).

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.

Phase I

Phase I trials are the first stage of testing in human subjects. Normally, a small group of 20–100 healthy volunteers/ informed consent will be recruited. This phase is designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug. These trials are often conducted in a clinical trial clinic, where the subject can be observed by full-time staff. These clinical trial clinics are often run by contract research organization (CROs) who conduct these studies on behalf of pharmaceutical companies or other research investigators. 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 best and safest dose can be found and to discover the point at which a compound is too poisonous to administer. The tested range of doses will usually be a fraction of the dose that caused 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 the treatment is likely to make healthy individuals ill. These studies are usually conducted in tightly controlled clinics called CPUs (Central Pharmacological Units), where participants receive 24-hour medical attention and oversight. In addition to the previously mentioned unhealthy individuals, "patients who have typically already tried and failed to improve on the existing standard therapies" may also participate in phase I trials. Volunteers are paid an inconvenience fee for their time spent in the volunteer centre. Pay depends on length of participation.

Informed consent

Informed Consent: A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form. The informed consent form will include information on the clinical trial process, including tests that may be conducted, known risks and benefits of experimental treatment, length of clinical trial, and clinical trial contact information.

There are different kinds of phase I trial:

SAD

In Single Ascending Dose studies, small groups of subjects receive a single dose of the drug while they are observed and tested for a period of time. If tolerated, and the pharmacokinetic data is broadly in line with predicted safe values, the next group of subjects receives a higher dose. This is continued until pre-calculated pharmacokinetic safety levels are reached, or until the administered dose is associated with unacceptable toxicity. The maximally

tolerated dose (MTD) is usually the dose below the one that produces unacceptable toxicity. The MTD is also defined as the dose that has an acceptable number of side effects and is therefore used in further studies.

MAD

Multiple Ascending Dose studies follow the SAD studies both temporally and in process, as these allow determination of MTDs with repeat dosing. MAD studies assess the pharmacokinetics and pharmacodynamics of multiple doses of the drug: patients receive 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.

This phase will take up to 1year and max 70% of experimental drug pass over this phase.

Food effect

An investigation into any differences in absorption of the drug by the body, caused by eating before the drug is given. These studies are often 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 a dose or range of doses is determined, the next goal is to evaluate whether the drug has any biological activity or effect. Phase II trials are performed on larger groups (100-300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments in a larger group of volunteers and patients. Genetic testing is common, particularly when there is evidence of variation in metabolic rate. 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.

The goals of phase II studies are:

1. To learn more about safety and side effects
2. To provide data allowing selection of optimal doses for subsequent trials
3. Know within a short period of time whether the drug is likely to be effective.

Phase II trials also serve as pilot (or feasibility) studies, assessing whether a phase III trial is likely to be successful.

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

Phase II are blinded studies both researcher and volunteer subjects do not know who receives experimental drug or placebo only sponsor knows. 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 controlled 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. Some researchers argue that phase II studies are generally smaller than they ought to be.

It will take up to 2 years only 30% of experimental drug pass over this stage.

Placebo

A placebo is an inactive pill, liquid or powder that looks like the experimental treatment but has no effect on the body. In some clinical trials, experimental treatments are compared with placebos to evaluate the effectiveness of the experimental treatment.

Control group

A control group consists of participants who receive either standard treatment or a placebo and serves as a comparison group to measure the effectiveness of the experimental treatment other participants are receiving. Participants are randomly assigned to control or non-control groups.

Single blind study

A single blind study is a clinical trial in which either the participant or the clinical trial team does not know if the participant is taking the experimental treatment.

Double blind study

A double blind study is a clinical trial in which both the participant and clinical trial team do not know which participants are receiving the experimental treatment and which are receiving a placebo or standard treatment.

Triple blind study

A triple blind study is a clinical trial in which all i.e. participant, clinical trial team and institution or CRO do not know which participants are receiving the experimental treatment and which are receiving a placebo or standard treatment only sponsors know.

Example Cancer Design

In the first stage, the investigator attempts to rule out drugs which have no or little biologic activity. For example, he may specify that a drug must have some minimal level of activity, say, in 20% of participants. If the estimated activity level is less than 20%, he chooses not to consider this drug further, at least not at that maximally tolerated dose. If the estimated activity level exceeds 20%, he will add more participants to get a better estimate of the response rate. A typical study for ruling out a 20% or lower response rate enters 14 participants. If no response is observed in the first 14 participants, the drug is considered not likely to have a 20% or higher activity level. The number of additional participants added depends on the degree of precision desired, but ranges from 10 to 20. Thus, a typical cancer phase II study might include fewer than 30 people to estimate the response rate.

Phase III

This phase is designed to assess the effectiveness of the new intervention and, thereby, its value in clinical practice. The percentage of Phase II trials that proceed to Phase III, as of 2008, is 18%. 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. Phase III trials of chronic conditions or diseases often have a short follow-up period for evaluation, relative to the period of time the intervention might be used in practice. This is sometimes called the "pre-marketing phase" because it actually measures consumer response to the drug.

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 categorized as "Phase IIIB studies."

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),

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 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 through a New Drug Application (NDA) containing all manufacturing, pre-clinical, and clinical data. 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.

Phase III studies allow an extensive evaluation of any side effects.

- Common efficacy endpoints include:
  - Mortality
  - Occurrence of the disease of interest
  - Disease progression
  - Cure or relief of chronic symptoms
  - Change in lifestyle or behavior.

Most trials have parallel groups: independent groups of subjects, where each subject receives only one treatment. In a crossover trial, each participant gets both treatments being tested. Some participants are assigned at random to receive drug A, and later, drug B. Others receive B, then A. Each subject serves as his/her own comparison: this is a common design for bioequivalence trials.

Orphan drug trials

Orphan drug trials test drugs designed to treat rare diseases – defined by the US FDA as affecting fewer than 200,000 Americans; the EU defines rare disease as one that affects less than 5 in 10,000. Some are rare genetic diseases that occur when missing or defective enzymes prevent essential biochemical reactions from happening. Because affected individuals are so few, an orphan drug may be tested only on a small number of participants, who generally are so sick that if the drug works, their improved health is obvious.

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. (eg after approval under FDA Accelerated Approval Program) 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).

Fig 3: Pharmacovigilance/post-marketing surveillance.

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).

Phase IV studies allow an;

1. Tpecial studies and long-term efficacy or effectiveness/use
2. The studies are designed to monitor
3. The impact on a person's quality of life
4. Cost-effectiveness of a therapy compared to other traditional and new therapies.

Recent regulatory reforms initiated by Central Drugs Standard Control Organization (CDSCO) Fast-tracking approval timelines: - [18, 20]

In September 2009, the CDSCO revised timelines for various

regulatory processes. If the application is complete, first response from the DCGI office can now be expected within 30 days for T licence and 45 days for approval of clinical trial applications. Moreover, applicants can check the status of their application since the approval letters sent out by the DCGI office are displayed on the CDSCO website under 'Daily Dispatch' section.

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