

**REVIEW - 2****An Overview of Clinical Research for Anesthesiologists**

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The process of drug development and regulation require much effort and co-operation between clinicians, pharmaceutical manufacturers and government regulators to achieve a common goal of development and utilization of safe and effective drugs. A fundamental understanding of this process may further facilitate optimal drug utilization and active involvement of clinician in the drug development process. This article reviews the process by which new drugs are introduced into practice with emphasis on pharmaceutical development and government regulation.

**CLINICAL TRIALS**

More than half of the original studies published in anesthesiology are clinical investigations. Most involve comparing the effects of various treatments or interventions on variables of interest to anesthesiologists, intensivists and pain medicine specialists. They, thus fall under the general heading of "clinical trials". A clinical trial is defined as a prospective study comparing the effect and value of intervention against a control in human beings. It may involve either simple or complex intervention or may involve testing a drug, a technique, new equipment or any new modality. In fact a clinical trial may involve anywhere from 10 - 10,000 subjects, may be carried out in multiple centers and it may be performed in volunteers instead of patients. While

undergoing the trial, the agent being tested is called an investigational new drug/equipment/technique.

In a clinical trial, the investigator first identifies the medication or device to be tested. Then the investigator decides what to compare it with (one or more existing treatments or a placebo), and what kind of patients might benefit from the medication/device. If the investigator cannot obtain enough patients with a specific disease or condition at his or her own location, then he or she assembles investigators at other locations who can obtain the same kind of patients to receive the treatment. 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. The researchers send the data to the trial sponsor, who then analyzes the pooled data using statistical tests. The important parties responsible in clinical research are shown in Figure 1.

Some examples of what a clinical trial may be designed to do are as follow:

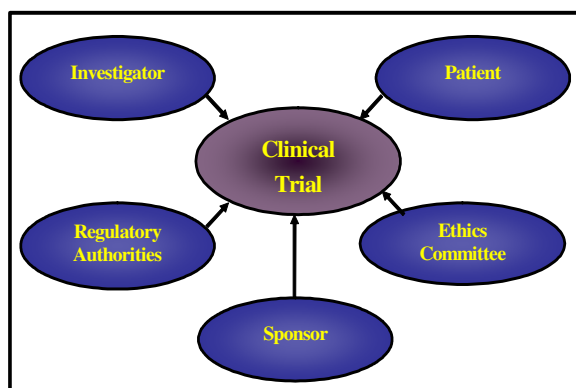
- Assess the safety and effectiveness of a new medication or device on a specific kind of patient.
- Assess the safety and effectiveness of a different dose of a medication than is commonly used.
- Assess the safety and effectiveness of an already marketed medication or device on a new kind of patient (who is not yet approved by regulatory authorities to be given the medication or device).
- 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.

While most clinical trials compare two medications or devices, some trials compare three or four medications, doses of medications, or devices against each other.

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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 (operating manual).



**Figure 1**

*Parties Involved in a Clinical Trial*

Clinical trials are required, before the national regulatory authority will approve marketing of the drug or device, or a new dose of the drug, for use on patients.

### PHASES OF CLINICAL TRIALS<sup>1</sup>

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

#### Phase 0:

Phase 0 trial is a recent designation for first stage of testing in human subjects. These trials are also known as human microdosing studies to establish very early whether the drug or agent behaves in human subjects as was expected from preclinical studies. A single subtherapeutic dose of study drug is administered to a small number of subjects

(10-15) to gather preliminary data on pharmacokinetics and pharmacodynamics of the drug. However, it gives no information on safety or efficacy of the drug. Questions have been raised about the usefulness of phase 0 trials and these are presently not performed in India.

#### Phase I:

Phase I trials are actually the first stage of testing performed in human subjects. Normally, a small (20-80) group of healthy volunteers will be selected. This phase includes trials designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug. The tested range of doses will usually be a fraction of the dose that causes harm in animal testing. 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 most often include healthy volunteers. However, there are some circumstances when real patients are used, such as patients who have end-stage disease and lack other treatment options like oncology (cancer) and HIV drug trials. Volunteers are paid compensation for their time spent in the volunteer centre.

#### 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. During phase II trials when the drug is discovered not to work as planned or is found to be having toxic effects, the development process for the drug fails.

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), whereas 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. Study on CNS 7056, an anesthetic/sedative, which acts on GABA receptors is in phase II trial. Three doses of this drug are being compared to Midazolam in patients undergoing GI endoscopy.

#### 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. Randomization, a strategy that is used to minimize bias in

clinical trials, consists of two distinct operations: random allocation and a appropriate method of randomization. Random allocation refers to the assignment of patient to treatments such that chances of receiving any one treatment are the same for all comparative treatments. Randomization sequence that provides an appropriate method of randomization are based on random number tables, computer programme or any other technique for which the chance that any single treatment is assigned to a patient is the same for all comparative 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.

Once a drug is proved to be 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 give the sponsor approval to market the drug.

Presently in this phase of trial Sugammadex , a novel relaxant binding agent , has demonstrated the ability to reverse shallow as well as profound depth of block induced by rocuronium and other steroidal non-depolarizing neuromuscular blocking agents. Several factors associated with the use of sugammadex have yet to be determined, such as the efficacy and safety in patients with poorer health or in those with neuromuscular disorders, the incidence of infrequent adverse events in larger patient populations and the cost effectiveness of the drug relative to existing reversal agent .

#### **Phase IV:**

Phase IV trial is also known as Post Marketing Surveillance Trial. Phase IV trials like phase III are conducted in hospitals. These involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold. The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period. The recent experience of anesthesia community with Rapacuronium, which was found after release of the drug, to be associated with unacceptable high incidence of sometimes fatal bronchospasm, reinforces the importance of reporting even minor adverse effect .

Harmful effects discovered by Phase IV trials may result in a drug being no longer sold or restricted to certain uses. Rofecoxib was one of the most widely used drug to be

withdrawn from the market in phase IV trial. After approval from FDA, it was marketed in 1999 but because of the concerns about increased risk of heart attack and stroke associated with long term use and high dosage, it was withdrawn from market in 2004. Although pre approval phase III trials like APPORVA study showed no risk of adverse cardiovascular events for first eighteen months of its use . Similarly antidiabetic drug Troglitzone has been withdrawn because of risk of hepatotoxicity . Comparison of regional and general anesthesia for effects on neurodevelopmental outcome and apnea in infants is undergoing phase IV trial at present. LMX- 4 (4% lidocaine topical) which reduces pain and anxiety associated with venipuncture in pediatric age group has completed phase IV trial.

#### **BIOEQUIVALENCE STUDIE**

'Bioequivalence studies' is a term in pharmacokinetics used to assess the expected in vivo biological equivalence of two proprietary preparations of a drug.

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, can be expected to be essentially the same. Pharmaceutical equivalence implies that the same amount of the same active substance(s), in the same dosage form, and the same route of administration meets the same or comparable standards.

A bioequivalence study compares the bioavailability between a test drug product (to-be-marketed Generic product) and a reference drug product (commercially-available innovator product) whereby each of the preparations are administered in a cross-over study to volunteer subjects, generally healthy individuals but occasionally in patients. For a pharmacokinetic comparison, the plasma concentration data are used to assess key pharmacokinetic parameters such as area under the curve (AUC), peak concentration (C<sub>max</sub>), time to peak concentration (T<sub>max</sub>), and absorption lag time (t<sub>lag</sub>). Blood samples are obtained at regular intervals and assayed for parent drug (or occasionally metabolite) concentration. Occasionally, blood concentration levels are not possible to compare the two products (e.g. inhaled corticosteroids); in this case, pharmacodynamic endpoints rather than pharmacokinetic endpoints are used for comparison. Testing should be conducted at several different doses, especially when the drug displays non-linear pharmacokinetics. The statistical assessment of bioequivalence is based on the 90% confidence interval for the ratio of the test mean to the reference mean for AUC and C<sub>max</sub>.

## ETHICAL CONDUCT

Clinical trials are closely supervised by appropriate regulatory authorities. All studies that involve a medical or therapeutic intervention on human subjects (patients/healthy volunteers) must be approved by a supervising ethics committee before permission is granted to start the trial.

Researchers must obtain the full and informed consent of participating human subjects

Clinical studies should be carried out according to International Conference on Harmonization (ICH) / the World Health Organization (WHO) Good Clinical Practice standards. This provides a unified standard for the European Union (EU), Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and WHO. Thus, any country that adopts this guideline technically follows the same standard.

A Contract Research Organization (CRO) is an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and function and CROs are independent to offer their services to pharmaceutical companies .

Services offered by CROs include: product development and formulation, clinical trial management (preclinical through phase IV), central laboratory services for processing trial samples, data management services for preparation of an FDA New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA), and many other complementary services.

The trial is conducted in compliance with the currently approved protocol (including any amendments), as well as with Good Clinical Practice (GCP) and all other applicable regulatory requirement(s).

Research that is not conducted according to high standards of quality can yield invalid data and it is also unethical as it may put research participants at risk.

STANDARD OPERATING PROCEDURE (SOPS) "Write down what you do, do what is written down!"

Performing clinical trials is bound by regulations and good clinical practice, with the overriding concern of protecting the safety and welfare of study subjects. One of the best ways to ensure that all these conditions are met is to formulate and follow (SOPs).

In clinical research, SOPs are defined by the International Conference on Harmonization (ICH) as "detailed, written instructions to achieve uniformity of the performance of a specific function"-to achieve maximum safety and efficiency of the performed clinical research operations.

Standard operating procedures are just that: the "procedures" and "processes" that are used and "operate" are "standardized" to ensure that it is done the same way

each time. It is therefore a must that all people and sites involved in clinical studies (both at the sponsor and at the investigative sites) have appropriate SOPs in place in order to conduct clinical research and to ensure compliance with the current regulations.

## ADVANTAGES OF PARTICIPATION IN CLINICAL TRIALS

**For Health Care Providers:** The true value of participation in clinical research trials is the opportunity to advance medical science and patient care. A healthcare provider that conducts clinical research trials in an efficient, cost-effective manner also will have the opportunity to increase its level of participation in future trials and solidify its reputation as a cutting-edge provider in the highly competitive healthcare market.

The investigators have the opportunities to get first hand experience with the most recent drugs, which usually offer advances over existing therapies. Extensive training on global medical and clinical research practices is often imparted during the course of the project. They get global recognition as they are on the same platform as other international experts working on the project.

**For Patients or Volunteer:** Patients participating in clinical trials get free medical care, which includes costs of investigations and medicine. They are not bound in anyway to continue to participate in the trial, and may withdraw their consent at any time. Their participation in trials provides them with more frequent and focused consultations, with an obvious improvement in quality of healthcare.

Many pharmaceutical companies are willing to invest in infrastructure development in hospitals where clinical trials are conducted, Thus having obvious benefits for the hospital management.

## THE REGULATORY APPROVAL PROCESS IN INDIA

A Common Technical Document is proposed to simplify the work of regulatory authorities while reviewing data. Mutual recognition of cross-border data will be possible if uniform processes such as good clinical practice (GCP) and good laboratory practice (GLP) are followed while generating such data. The adaptation of such guidelines in India will certainly increase the credibility of Indian data and make it acceptable to regulatory authorities the world over. This is particularly important for indigenously developed drugs, to allow the developers access to global markets. Mutual recognition of data will reduce unnecessary duplication of research drug development costs. This in turn will allow populations to have early access to important medicines, perhaps at more affordable costs.

Clinical trials are regulated by the Drugs Controller

General of India (DCGI), who is now responsible for assuring that all clinical trials are ICH/GCP compliant. The DCGI approval process categorizes clinical trials into two types. If the study protocol has already been approved by the cognizant regulatory authorities in one or more developed countries (such as the U.S., Canada, U.K., Switzerland, Germany, Australia, Japan, and South Africa), the study is classified as a Type A trial and can be approved using a fast-track process within 2 to 6 weeks after the required documentation has been submitted. All other studies are classified as Type B. For these, the approval process is generally 8 to 12 weeks. It is also important to note that the institutional review board (IRB) approval process can be conducted in parallel with the DCGI review and, if import licenses are needed, the applications for these can also proceed in parallel. These provisions facilitate the process of getting the study protocols in place and initiating the trial. India's participation in early phase research facilitates early regulatory review of clinical data with the opportunity for the drug to enter the market at the same time as in developed countries.

### CONCLUSION

Globally, clinical research is becoming a thrust area. It is essential for development of not only new drugs but also for the development of new formulations, drug delivery systems, dosage regime, surgical and diagnostic techniques, devices and therapies. Clinical research can make available the state of art therapy for many deserving Indian patients who were hitherto deprived of such therapeutic advances. Anesthesia as a specialty interacts with many disciplines including surgery, obstetrics, neurology, pulmonology and critical care. This enables anesthesiologists to collaborate in clinical research with many disciplines. Clinical research attributable to investigator in our specialty is diverse and extends beyond the traditional field of anesthesia and critical care, thus giving anesthesiologists, as investigator the opportunity to get first hand experience with the most recent drug and global recognition as they are on same platform as others interventional experts working on the project. A fundamental knowledge of clinical research would lead to a definite improvement in hospital infrastructure, facilitation of optimal drug utilization (in terms of formulations, dosage, drug delivery systems) and active involvement of anesthesiologist in drug development process. It will also help in improvement of the quality of prospective clinical trials in

anesthesia with specific attention to area like trial methodology.

### REFERENCES

1. ClinicalTrials.gov - Information on Clinical Trials and Human Research Studies: glossary.
2. Chalmers TC, Celano P, Sacks HS, Smith H: Bias in treatment assignment in controlled clinical trials. *N Engl j Med* 1983; 309: 1358-61.
3. Pocock SJ, Hughes MD, Lee RJ: Statistical problems in reporting of clinical trials: A survey of three medical journals. *N Engl j Med* 1987; 317:426-32.
4. Altman DG: Randomization: Essential for reducing bias (letter). *Br Med J* 1991; 302: 1481-2.
5. Stewart LA, Parmar MKB: Bias in the analysis and reporting of randomized controlled trials. *J tech assess health Care* 1996; 12: 264-75.
6. Browner WS: Clinical research: A simple recipe of doing it well. *Anesthesiology* 1994; 80: 923-8.
7. Yang LP, Keam SJ Sugammadex: a review of its use. *Drugs*.2009; 69: 919-42.
8. Goudsouzian NG: Rapacuronium and bronchospasm. *Anesthesiology* 2001; 94: 727-8.
9. Kron S: Severe bronchospasm and desaturation in a child associated with rapacuronium. *Anesthesiology* 2001; 94: 923-4.
10. Naguib M: How serious is the bronchospasm induced by rapacuronium. *Anesthesiology* 2001; 94: 924-5.
11. Meakin GH, Pronske EH, Lerman J et al : Bronchospasm after rapacuronium in infants and children. *Anesthesiology* 2001; 94: 926-7.
12. Bresalier RS, Sandler RS, Quan H, et al. "Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial". *N Engl j Med* 2005; 352: 1092-102.
13. Merck Announces Voluntary Worldwide Withdrawal of VIOXX" (pdf). [http://www.merck.com/newsroom/vioxx/pdf/vioxx\\_press\\_release\\_final.pdf](http://www.merck.com/newsroom/vioxx/pdf/vioxx_press_release_final.pdf). Retrieved 2008-04-16.
14. Michael P. Stern On the Need for Outcome Trials in Preventive Pharmacology Lessons from the recent experience with adverse drug reactions *Diabetes Care* 1999; 22: 844-45.
15. CDSCO guidelines for Bioavailability and Bioequivalence studies.
16. ICH Topic E 6 (R1) Guideline for Good Clinical Practice.
17. Schedule Y (Amended Version-2005), Central Drugs Standard Control Organization.