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Review Article

A Comprehensive Review on Clinical Trials in India

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ABSTRACT
A clinical trial is a research study in human volunteers to answer specific health questions. Carefully conducted clinical trials are fastest and safest way to find treatment that work in people and way to improve health. Investigational trials determine whether experimental treatment or new ways of using known therapies are safe and effective under controlled environment. Observational trials address health issues in large groups of people or population in natural settings. Clinical trials aim to measure therapeutic effectiveness and constitute an important and highly specialized form of biological assay. In phase-I pharmacokinetics, safety, gross effects are studied on human volunteers, by clinical pharmacologists. If the drug passes the test, it enters phase II testings, where pharmacokinetics, safety, therapeutic efficiency are studied on selected patients by clinical pharmacologist, if passes hundreds of selected patients are now studied, primarily for safety and therapeutic effectiveness by clinical investigators in phase III. If this is passed the drug is now approved and marketed. Even after marketing, physicians from various hospitals and clinics send their opinion about the drug, regarding ADR, efficacy in phase IV.

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INTRODUCTION
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 disease1. For any new drug to enter in clinical trial, it must pass preclinical studies. Preclinical studies involve *in vitro* (i.e. test-tube or Laboratory) studies and trials on animal populations. Wide range of dosages of the study drug is given to animal subjects or to an in-vitro substrate in order to obtain preliminary efficacy, toxicity and pharmacokinetic information.

Background and Purpose
The efficacy and safety of medicinal products should be demonstrated by clinical trials which follow the guidance in 'Good Clinical Practice: Consolidated Guideline' (ICH E6) adopted by the ICH, 1 May 1996. The role of statistics in clinical trial design and analysis is acknowledged as essential in that ICH guideline. The proliferation of statistical research in the area of clinical trials coupled with the critical role of clinical research in the drug approval process and health care in general necessitate a succinct document on statistical issues related to clinical trials. This guidance is written primarily to attempt to harmonise the principles of statistical methodology applied to clinical trials for marketing applications submitted in Europe, Japan and the United States.

As a starting point, this guideline utilised the CPMP (Committee for Proprietary Medicinal Products) Note for Guidance entitled 'Biostatistical Methodology in Clinical Trials in Applications for Marketing Authorisations for Medicinal Products' (December, 1994). It was also influenced by 'Guidelines on the Statistical Analysis of Clinical Studies' (March, 1992) from the Japanese Ministry of Health and Welfare and the U.S. Food and Drug Administration document entitled 'Guideline for the Format and Content of the Clinical and Statistical Sections of

a New Drug Application' (July, 1988). Some topics related to statistical principles and methodology is also embedded within other ICH guidelines, particularly those listed below. The specific guidance that contains related text will be identified in various sections of this document.

E1A: The Extent of Population Exposure to Assess Clinical Safety

E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

E2B: Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports

E2C: Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs

E3: Structure and Content of Clinical Study Reports

E4: Dose-Response Information to Support Drug Registration

E5: Ethnic Factors in the Acceptability of Foreign Clinical Data

E6: Good Clinical Practice: Consolidated Guideline

E7: Studies in Support of Special Populations: Geriatrics

E8: General Considerations for Clinical Trial

E10: Choice of Control Group in Clinical Trials

M1: Standardisation of Medical Terminology for Regulatory Purposes

M3: Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

This guidance is intended to give direction to sponsors in the design, conduct, analysis, and evaluation of clinical trials of an investigational product in the context of its overall clinical development. The document will also assist scientific experts charged with preparing application summaries or assessing evidence of efficacy and safety, principally from clinical trials in later phases of development.

CONSIDERATIONS FOR OVERALL CLINICAL DEVELOPMENT

Trial Context

Development Plan The broad aim of the process of clinical development of a new drug is to find out whether there is a dose range and schedule at which the drug can be shown to be simultaneously safe and effective, to the extent that the risk-benefit relationship is acceptable. The particular subjects, who may benefit from the drug, and the specific indications for its use, also need to be defined.

Satisfying these broad aims usually requires an ordered programme of clinical trials, each with its own specific objectives (see ICH E8). This should be specified in a clinical plan, or a series of plans, with appropriate decision points and flexibility to allow modification as knowledge accumulates. A marketing application should clearly describe the main content of such plans, and the contribution made by each trial. Interpretation and assessment of the evidence from the total programme of trials involves synthesis of the evidence from the individual trials. This is facilitated by ensuring that common standards are adopted for a number of features of the trials such as dictionaries of medical terms, definition and timing of the main measurements, handling of protocol deviations and so on. A statistical summary, overview or meta-analysis may be informative when medical questions are addressed in more than one trial. Where possible this should be envisaged in the plan so that the relevant trials are clearly identified and any necessary common features of their designs are specified in advance. Other major statistical issues that are expected to affect a number of trials in a common plan should be addressed in that plan.

Confirmatory Trial

A confirmatory trial is an adequately controlled trial in which the hypotheses are stated in advance and evaluated. As a rule, confirmatory trials are necessary to provide firm evidence of efficacy or safety. In such trials the key hypothesis of interest follows directly from the trial's primary objective, is always pre-defined, and is the hypothesis that is subsequently tested when the trial is complete. In a confirmatory trial it is equally important to estimate with due precision the size of the effects attributable to the treatment of interest and to relate these effects to their clinical significance.

Confirmatory trials are intended to provide firm evidence in support of claims and hence adherence to protocols and standard operating procedures is particularly important; unavoidable changes should be explained and documented, and their effect examined. A justification of the design of each such trial, and of other important statistical aspects such as the principal features of the planned analysis, should be set out in the protocol. Each trial should address only a limited number of questions.

Firm evidence in support of claims requires that the results of the confirmatory trials demonstrate that the investigational product under test has clinical benefits. The confirmatory trials should therefore be sufficient to answer each key clinical question relevant to the efficacy or safety

claim clearly and definitively. In addition, it is important that the basis for generalisation to the intended patient population is understood and explained; this may also influence the number and type (e.g. specialist or general practitioner) of centres and/or trials needed. The results of the confirmatory trial(s) should be robust. In some circumstances the weight of evidence from a single confirmatory trial may be sufficient

Exploratory Trial

The rationale and design of confirmatory trials nearly always rests on earlier clinical work carried out in a series of exploratory studies. Like all clinical trials, these exploratory studies should have clear and precise objectives. However, in contrast to confirmatory trials, their objectives may not always lead to simple tests of pre-defined hypotheses. In addition, exploratory trials may sometimes require a more flexible approach to design so that changes can be made in response to accumulating results. Their analysis may entail data exploration; tests of hypothesis may be carried out, but the choice of hypothesis may be data dependent. Such trials cannot be the basis of the formal proof of efficacy, although they may contribute to the total body of relevant evidence.

Any individual trial may have both confirmatory and exploratory aspects. For example, in most confirmatory trials the data are also subjected to exploratory analyses which serve as a basis for explaining or supporting their findings and for suggesting further hypotheses for later research. The protocol should make a clear distinction between the aspects of a trial which will be used for confirmatory proof and the aspects which will provide data for exploratory analysis.

Scope of Trials

Population

In the earlier phases of drug development the choice of subjects for a clinical trial may be heavily influenced by the wish to maximise the chance of observing specific clinical effects of interest, and hence they may come from a very narrow subgroup of the total patient population for which the drug may eventually be indicated. However by the time the confirmatory trials are undertaken, the subjects in the trials should more closely mirror the target population. Hence, in these trials it is generally helpful torelax the inclusion and exclusion criteria as much as possible within the target population, while maintaining sufficient homogeneity to permit precise estimation of treatment effects. No individual clinical trial can be expected to be totally representative of future users, because of the possible influences of geographical location, the time when it is conducted, the medical practices of the particular investigator(s) and clinics, and so on. However the influence of such factors should be reduced wherever possible, and subsequently discussed during the interpretation of the trial results.

Primary and Secondary Variables

The primary variable (‘target’ variable, primary endpoint) should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial. There should generally be only one primary variable. This will usually be an efficacy variable, because the primary objective of most confirmatory trials is to provide strong scientific evidence regarding efficacy. Safety/tolerability may sometimes be the primary variable, and will always be an important consideration. Measurements relating to quality of life and health economics are further potential primary variables. The selection of the primary variable should reflect the accepted norms and standards in the relevant field of research. The use of a reliable and validated variable with which experience has been gained either in earlier studies or in published literature is recommended. There should be sufficient evidence that the primary variable can provide a valid and reliable measure of some clinically relevant and important treatment benefit in the patient population described by the inclusion and exclusion criteria. The primary variable should generally be the one used when estimating the sample size

In many cases, the approach to assessing subject outcome may not be straightforward and should be carefully defined. For example, it is inadequate to specify mortality as a primary variable without further clarification; mortality may be assessed by comparing proportions alive at fixed points in time, or by comparing overall distributions of survival times over a specified interval. Another common example is a recurring event; the measure of treatment effect may again be a simple dichotomous variable (any occurrence during a specified interval), time to first occurrence, rate of occurrence (events per time units of observation), etc.

The assessment of functional status over time in studying treatment for chronic disease presents other challenges in selection of the primary variable. There are many possible approaches, such as comparisons of the assessments done at the beginning and end of the interval of observation, comparisons of slopes calculated

from all assessments throughout the interval, comparisons of the proportions of subjects exceeding or declining beyond a specified threshold, or comparisons based on methods for repeated measures data. To avoid multiplicity concerns arising from post hoc definitions, it is critical to specify in the protocol the precise definition of the primary variable as it will be used in the statistical analysis. In addition, the clinical relevance of the specific primary variable selected and the validity of the associated measurement procedures will generally need to be addressed and justified in the protocol

Composite Variables

If a single primary variable cannot be selected from multiple measurements associated with the primary objective, another useful strategy is to integrate or combine the multiple measurements into a single or 'composite' variable, using a predefined algorithm. Indeed, the primary variable sometimes arises as a combination of multiple clinical measurements (e.g. the rating scales used in arthritis, psychiatric disorders and elsewhere). This approach addresses the multiplicity problem without requiring adjustment to the type I error. The method of combining the multiple measurements should be specified in the protocol, and an interpretation of the resulting scale should be provided in terms of the size of a clinically relevant benefit. When a composite variable is used as a primary variable, the components of this variable may sometimes be analysed separately, where clinically meaningful and validated. When a rating scale is used as a primary variable, it is especially important to address such factors as content validity, inter- and intra-rater reliability and responsiveness for detecting changes in the severity of disease.

Global Assessment Variables

Global assessment variables generally have a subjective component. When a global assessment variable is used as a primary or secondary variable, fuller details of the scale should be included in the protocol with respect to:

1) the relevance of the scale to the primary objective of the trial;

2) the basis for the validity and reliability of the scale;

3) how to utilise the data collected on an individual subject to assign him/her to a unique category of the scale;

4) how to assign subjects with missing data to a unique category of the scale, or otherwise evaluate them.

If objective variables are considered by the investigator when making a global assessment, then those objective variables should be considered as additional primary, or at least important secondary, variables. Global assessment of usefulness integrates components of both benefit and risk and reflects the decision making process of the treating physician, who must weigh benefit and risk in making product use decisions. A problem with global usefulness variables is that their use could in some cases lead to the result of two products being declared equivalent despite having very different profiles of beneficial and adverse effects

Multiple Primary Variables

It may sometimes be desirable to use more than one primary variable, each of which (or a subset of which) could be sufficient to cover the range of effects of the therapies. The planned manner of interpretation of this type of evidence should be carefully spelled out. It should be clear whether an impact on any of the variables, some minimum number of them, or all of them, would be considered necessary to achieve the trial objectives. The primary hypothesis or hypotheses and parameters of interest (e.g. mean, percentage, and distribution) should be clearly stated with respect to the primary variables identified, and the approach to statistical inference described. The effect on the type I error should be explained because of the potential for multiplicity problems (see Section 5.6); the method of controlling type I error should be given in the protocol. The extent of intercorrelation among the proposed primary variables may be considered in evaluating the impact on type I error. If the purpose of the trial is to demonstrate effects on all of the designated primary variables, then there is no need for adjustment of the type I error, but the impact on type II error and sample size should be carefully considered.

PHASES OF CLINICAL TRIAL

Before pharmaceutical companies start clinical trials on a drug, they conduct extensive pre-clinical studies3.

Pre-clinical studies Pre-clinical studies involve in vitro (i.e., test tube or laboratory) studies and trials on animal populations. Wideranging 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 worthwhile to go ahead with further testing.

Phase 0

Phase 0 is a recent designation for exploratory,

first-inhuman trials conducted in accordance with the U.S. Food and Drug Administration's (FDA) 2006 Guidance on Exploratory

Investigational New Drug (IND) Studies Phase 0 trials 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 anticipated 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

Phase I

Phase I trials are the first stage of testing 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. 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 end-stage disease and lack other treatment options. This exception to the rule most often occurs in oncology (cancer) and HIV drug trials. 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 precalculated 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

MAD

Multiple Ascending Dose studies are conducted to better understand the pharmacokinetics & pharmacodynamics of multiple doses of the drug.

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

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), 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.

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.

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 (FDA (USA), TGA (Australia), EMEA (European Union), etc.).

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 authoritiesin different countries.

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.

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).

Investigational New Drug (Ind) / Clinical Trial Exception (Ctx) / Clinical Trial Authorization (Cta) Application

INDs (in the U.S.), CTXs (in the U.K.) and CTAs (in Australia) are examples of requests submitted to appropriate regulatory authorities for permission to conduct investigational research. This research can include testing of a new dosage form or new use of a drug already approved to be marketed.

In addition to obtaining permission from appropriate regulatory authorities, an Institutional or Independent Review Board (IRB) OR Ethical Advisory Board must approve the protocol for testing as well as the informed consent documents that volunteers sign prior toparticipating in a clinical study. An IRB is an independent committee of physicians, community advocates and others that ensures a clinical trial is ethical and the rights of study participants are protected

ICH GCP GUIDELINES

The principals of ICH GCP

1. Clinical trial should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement.
2. 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.
3. The rights, safety, and well being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial. 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 / favorable 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 tasks
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 requiremen.
11. Investigational products should be manufactured, handled, and stored in accordance with applicable

Role of Pharmacists in Clinical Trial

Pharmacists have an active role to play in research and clinical trials first of all, we provide the necessary facilities required for proper storage of the investigational medicinal products (IMPs), either in the fridge or atcontrolled room temperature. Regular temperature monitoring is ensured and recorded.

It is also the pharmacist's duty to ensure there is constant supply of IMPs at all times, and that

they are dispensed to patients accordingly. Patients are counselled on the correct use of the IMPs in addition to any written information that is provided, such as, Informed Consent Form or the Patient Information Leaflet. IMPs returns from patients are counted and documented to determine compliance to the treatment. For inject able IMPs, pharmacists will also ensure that they are prepared in accordance to the specifications stipulated in the trial, and that they are administered appropriately.

Besides managing clinical trials, oncology pharmacists often run research projects that are aimed at improving outcomes in patients who receive medications, such as chemotherapy or other supportive drugs like anti-emetics, blood growth factor injections, etc.

Drug Utilization Evaluations (DUEs) are research projects that are commonly conducted by pharmacists. These projects aim to facilitate rational use of drugs within our patients. Essentially, providing insights on how drugs are used in patients and observing prescribing patterns by our physicians. DUEs are sometimes considered as drug audits because pharmacists are ensuring the use of medication is appropriate.

In addition, pharmacists also conduct observational surveys that are aimed at investigating patients' or physicians' perspectives and attitudes towards medications. Results obtained from surveys are used to improve the services that we provide to our patients. Currently, NCC's oncology pharmacy is conducting two surveys. They are aimed at investigating patients' use of complementary and alternative medications and on patients' perspective on safe handling of oral anti-cancer drugs. Very often, pharmacy students who are adequately trained to conduct research are assigned to survey the patients. We would like to take this opportunity to thank all our patients who have consented to participate in the survey

Risks and Benefits of Trials

Clinical trials are carefully designed to minimise the risks and maximise the benefits to all who take part, whatever treatment they receive. Some trials will have very little risk involved. However, the risks of a trial may be greater when less is known about the treatment being tested. Before any drugs are first given to people, they will have been developed in a laboratory and checked for safety in animals.

In all trials the treatment may cause side effects that doctors cannot predict and that you may not be expecting. These may be unpleasant and very rarely can be life-threatening. You should be told everything that the researchers know about any possible risks and side effects and why the trial is necessary so that you can make an informed choice about whether to take part.

CONCLUSION

A clinical trial for any new drug follows under the guidelines of ICH and GCP, clinical trial are conducted inhuman volunteers for confirmation of useful properties of new drug. After preclinical development, investigational new drug passes through clinical phases I, II, III and IV. These phases provide in detail explanation of pharmacokinetic, pharmacodynamic profile and side effect which may be harmful or beneficial, adverse effect and post marketing surveillance.

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