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Role of Post Approval Clinical Trials for Drug Safety in India

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A B S T R A C T

Clinical trials are prospective biomedical or behavioral research studies on human subjects that are designed to answer specific questions about biomedical or behavioral interventions (novel vaccines, drugs, treatments, functional foods, dietary supplements, devices or new ways of using known interventions), generating safety and efficacy data. Developing a new drug requires great amount of research work in chemistry, manufacturing, controls, preclinical science and clinical trials. Drug reviewers in regulatory agencies around the world bear the responsibility of evaluating whether the research data support the safety, effectiveness and quality control of a new drug product to serve the public health. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. As positive safety and efficacy data are gathered, the number of patients typically increases. Clinical trials can vary in size, and can involve a single research entity in one country or multiple entities in multiple countries. A full series of trials may cost hundreds of millions of dollars. The burden of paying is usually borne by the sponsor, which may be a governmental organization or a pharmaceutical, biotechnology or medical device company. When the required support exceeds the sponsor's capacity, the trial may be managed by an outsourced partner, such as a contract research organization or an academic clinical trials unit. EU pharmaceutical legislation requires the European Medicines Agency (EMA), which maintains the Eudra CT database on behalf of EU member states to provide information held in EudraCT to the public. This is described in article 57 of Regulation (EC) No 726/2004 and article 41 of the Paediatric Regulation (EC) No 1901/2006. Together, they established that data on clinical trials conducted in adults and in paediatric populations be made public.

Keywords: Clinical trials, Various phases, Drug, FDA, DGCA

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

The history of Good Clinical Practice (GCP) statute traces back to one of the oldest enduring traditions in the history of medicine: The Hippocratic Oath. As the guiding ethical code it is primarily known for its edict to do no harm to the patient. However, the complexities of modern medicine research necessitate a more elaborate set of guidelines that address a Physician's ethical and scientific responsibilities such as obtaining informed consent or disclosing risk while involved in biomedical research. Good Clinical Practice is a set of guidelines for biomedical studies which encompasses the design, conduct, termination, audit, analysis, reporting and documentation of the studies involving human subjects. The fundamental tenet of GCP is that in research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the study subject. It aims to ensure that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical substances under investigation are properly documented. The guidelines seek to establish two cardinal principles: protection of the rights of human subjects and authenticity of biomedical data generated. These guidelines have been evolved with consideration of WHO, ICH, USFDA and European GCP guidelines as well as the Ethical Guidelines for Biomedical research on Human Subjects issued by the Indian Council of Medical Research. They should be followed for carrying out all biomedical research in India at all stages of drug development, whether prior or subsequent to product registration in India1.

Clinical trials are prospective biomedical or behavioral research studies on human subjects that are designed to answer specific questions about biomedical or behavioral interventions (novel vaccines, drugs, treatments, functional foods, dietary supplements, devices or new ways of using known interventions), generating safety and efficacy data. They are conducted only after satisfactory information has been gathered that satisfies health authority/ethics committee approval in the country where approval of the therapy is sought. Depending on product type and development stage, investigators initially enroll volunteers and/or patients into small pilot studies, and subsequently conduct progressively larger scale comparative studies. As positive safety and efficacy data are gathered, the number of patients typically increases. Clinical trials can vary in size, and can involve a single research entity in one country or multiple entities in multiple countries.

2. Clinical Trials an Overview

The first proper clinical trial was conducted by the physician James Lind. The disease scurvy, now known to be caused by a Vitamin C deficiency, would often have terrible effects on the welfare of the crew of long distance voyages. In 1740, the catastrophic result of Anson's circumnavigation attracted much attention in Europe; out of 1900 men, 1400 had died, most of them allegedly from having contracted scurvy. John Woodall, an English military surgeon of the British East India Company, had recommended the consumption of citrus fruit (it has an antiscorbutic effect) from the 17th century, but their use did not become widespread4. Lind conducted the first systematic clinical trial in 1747.He included a dietary supplement of an acidic quality in the experiment after two months at sea, when the ship was already afflicted with scurvy. He divided twelve scorbutic sailors into six groups of two. They all received the same diet but, in addition, group one was given a quart of cider daily, group two twenty-five drops of elixir of vitriol (sulfuric acid), group three six spoonfuls of vinegar, group four half a pint of seawater, group five received two oranges and one lemon, and the last group a spicy paste plus a drink of barley water. The treatment of group five stopped after six days when they ran out of fruit, but by that time one sailor was fit for duty while the other had almost recovered. Apart from that, only group one also showed some effect of its treatment.

After 1750 the discipline began to take its modern shape.John Haygarth demonstrated the importance of a control group for the correct identification of the placebo effect in his celebrated study of the ineffective remedy called Perkin's tractors. Further work in that direction was carried out by the eminent physician Sir William Gull, 1st Baronet in the 1860s.

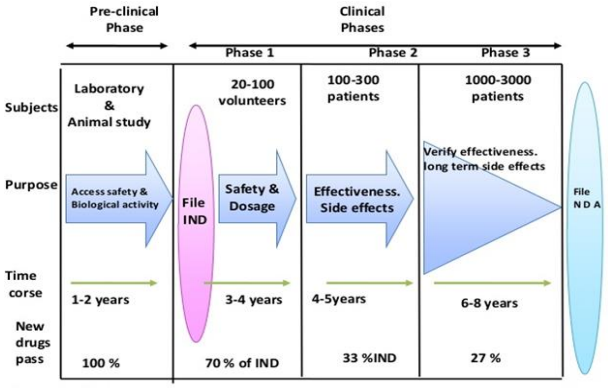

Fig 1: Clinical and pre-clinical phases

3. Phases of Clinical Trials

Clinical trials involving new drugs are commonly classified into four phases. Clinical trials of drugs may not fit into a single phase. For example, some may blend from phase I to phase II or from phase II to phase III. Therefore, it may be easier to think of early phase studies and late phase studies. 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.

A systematic verification of the study, carried out by persons not directly involved, such as:

(a) Study related activities to determine consistency with the Protocol

(b) Study data to ensure that there are no contradictions on Source Documents. The audit should also compare data on the Source Documents with the interim or final report.

It should also aim to find out if practices were employed in the development of data that would impair their validity.

(c) Compliance with the adopted Standard Operating Procedures (SOPs)

Clinical Trials in India: Advantages And Challenges:

In addition to the efforts mentioned above to align India's regulatory framework and guidelines with international standards, the main advantages of carrying out clinical trials are:

- ✓ Strong availability of study subjects across major therapeutic segments;
- ✓ High level of ICH GCP and US Food and Drug Administration standards compliance (since 2001, the DCGI has implemented conformity to ICH GCP and good laboratory practice guidelines. Generally, most competent authorities, including the US FDA, will find the standards of Indian clinical trials acceptable);
- ✓ High quality of research professionals (India has a strong reputation for graduating students in the medical and scientific fields. The government is involved in curriculum development at major universities and students pursuing these fields of study are given financial incentives to study in India);
- ✓ A favorable regulatory environment that allows the conduct of global trials, duty-free imports of drugs intended for use in trials, bioequivalence studies for export of data, etc;
- ✓ Cost competitiveness (depending on the number of patients and investigators, and the amount of analytical work completed in India, most sponsors will enjoy a 30-50% cost advantage over a similar trial in Europe or the US6).
- ✓ Increasing prevalence of diseases.
- ✓ Approval of clinical trial documents from both the IRB/IEC and the DCGI is mandatory to initiate a study. Because India's potential as a major hub for global clinical research has been acknowledged and thus, the regulatory bodies have to elevate themselves to meet international standards, they are facing some challenges. Some of the major issues that have been recognised as areas in need of improvement are discussed below.

4. Prerequisites for the Study

Investigational Pharmaceutical Product:

Physical, chemical, pharmaceutical properties and the formulation of the Investigational Product must be documented to permit appropriate safety measures to be taken during the course of a study. Instructions for the storage and handling of the dosage form should be documented. Any structural similarities to the other known compounds should be mentioned.

Pre-clinical supporting data:

The available pre-clinical data and clinical information on the Investigational Product should be adequate and convincing to support the proposed study.

Protocol:

A well designed study relies predominantly on a thoroughly considered, well-structuredand complete protocol.

1. Relevant components of Protocol
2. General information

a. Protocol title, protocol identifying number and date. All amendments should bear amendment number and date(s)

b. Name, address & contact numbers of the sponsor and the monitor / CRO

c. Name and title of the persons authorized to sign the protocol and the protocol amendments for the sponsor

d. Name, title, address and contact numbers of the sponsor's medical expert for the study

e. Name(s), title(s), address (es) and contact numbers of the investigator(s) who is / are responsible for conducting the study, along with their consent letter(s)

f. Name(s), address (es) and contact numbers of the institution(s) clinical laboratories and / or other medical and technical departments along with the particulars of the head(s) of the institution(s) and the relevant department(s).

5. Ethical & Safety Considerations

Ethical Principles:

All research involving human subjects should be conducted in accordance with the ethical principles contained in the current revision of Declaration of Helsinki (see Appendix 1) and should respect three basic principles, namely justice, respect for persons, beneficence (to maximize benefits and to minimize harms and wrongs) and non malaficence (to do no harm) as defined by "Ethical Guidelines for Biomedical Research on Human Subjects" issued by the Indian Council of Medical Research and any other laws and regulations of the country, which ensure a greater protection for subjects.

The following principles are to be followed:

a. Principles of essentiality whereby, the research entailing the use of human subjects is considered to be absolutely essential after a due consideration of all alternatives in the light of the existing knowledge in the proposed area of research and after the proposed research has been duly vetted and considered by an appropriate and responsible body of persons who are external to the particular research and who, after careful consideration, come to the conclusion that the said research is necessary for the advancement of knowledge and for the benefit of all members of the human species and for the ecological and environmental wellbeing of the planet.

b. Principles of voluntariness, informed consent and community agreement whereby, Study Subjects are fully apprised of the Study and the impact and risk of such Study on the Study Subjects and others; and whereby the research subjects retain the right to abstain from further participation in the research irrespective of any legal or other obligation that may have been entered into by them or by someone on their behalf, subject to only minimal restitute obligations of any advance consideration received and outstanding.

c. Principles of non-exploitation whereby as a general rule, research subjects are remunerated for their involvement in the research or experiment; and, irrespective of the social and economic condition or status, or literacy or educational levels attained by the research subjects kept fully apprised of all the dangers arising in and out of the research so that

they can appreciate all the physical and psychological risks as well as moral implications of the research whether to themselves or others, including those yet to be born.

d. Principles of privacy and confidentiality whereby, the identity and records of the human subjects of the research or experiment are as far as possible kept confidential; and that no details about identity of said human subjects, which would result in the disclosure of their identity, are disclosed without valid scientific and legal reasons which may be essential for the purposes of therapeutics or other interventions, without the specific consent in writing of the human subject concerned, or someone authorized on their behalf; and after ensuring that the said human subject does not suffer from any form of hardship, discrimination or stigmatization as a consequence of having participated in the research or experiment.

e. Principles of precaution and risk minimization whereby due care and caution is taken at all stages of the research and experiment (from its inception as a research idea, its subsequent research design, the conduct of the research or experiment and its applicative use) to ensure that the research subject and those affected by it are put to the minimum risk, suffer from no irreversible adverse effects and, generally, benefit from and by the research or experiment.

f. Principles of professional competence whereby, the research is conducted at all times by competent and qualified persons, who act with total integrity and impartiality and who have been made aware of, and mindful of, the ethical considerations to be borne in mind in respect of such Study.

g. Principles of accountability and transparency whereby, the research or experiment will be conducted in a fair, honest, impartial and transparent manner, after full disclosure is made by those associated with the Study of each aspect of their interest in the Study, and any conflict of interest that may exist; and whereby, subject to the principles of privacy and confidentiality and the rights of the researcher, full and complete records of the research inclusive of data and notes are retained for such reasonable period as may be prescribed or considered necessary for the purposes of post-research monitoring, evaluation of the research, conducting further research (whether by the initial researcher or otherwise) and in order to make such records available for scrutiny by the appropriate legal and administrative authority, if necessary.

h. Principles of the maximization of the public interest and of distributive justice whereby, the research or experiment and its subsequent applicative use are conducted and used to benefit all human kind and not just those who are socially better off but also the least advantaged; and in particular, the research subject themselves.

- ✓ Principles of institutional arrangements whereby, there shall be a duty on all persons connected with the research to ensure that all the procedures required to be complied with and all institutional arrangements required to be made in respect of the research and its subsequent use or application are duly made in a bonafide and transparent manner; and to take all appropriate steps to ensure that research reports, materials and data connected with the research are duly preserved and archived.
- ✓ Principles of public domain whereby, the research and any further research, experimentation or evaluation in response to, and emanating from such research is brought into the public domain so that its results are generally made known through scientific and other publications subject to such rights as are available to the researcher and those associated with the research under the law in force at that time.
- ✓ Principles of totality of responsibility whereby the professional and moral responsibility, for the due observance of all the principles, guidelines or prescriptions laid down generally or in respect of the research or experiment in question, devolves on all those directly or indirectly connected with the research or experiment including the researchers, those responsible for funding or contributing to the funding of the research, the institution or institutions where the research is conducted and the various persons, groups or undertakings who sponsor, use or derive benefit from the research, market the product (if any) or prescribe its use so that, inter alia, the effect of the research or experiment is duly monitored and constantly subject to review and remedial action at all stages of the research and experiment and its future use.
- ✓ Principles of compliance whereby, there is a general and positive duty on all persons, conducting, associated or connected with any research entailing the use of a human subject to ensure that both the letter and the spirit of these guidelines, as well as any other norms, directions and guidelines which have been specifically laid down or prescribed and which are applicable for that area of research or experimentation, are scrupulously observed and duly complied with.

6. Conclusion

Some issues about healthy volunteer recruitment in first-in-man trials and reimbursement remain unresolved, and they can be summarized as follows: (1) There is a lack of international consensus on the definition of healthy status, based on standard physical, psychological, and laboratory parameters, suitable for the enrolment of candidate subjects in first-in-man trials. (2) There is a need for guidelines about appropriate advertisements addressed to potential participants in first-in-man clinical trials, to set out specific ethical limitations. (3) There is a lack of international and/or local statements about standard criteria for offering fair payments to healthy volunteers enrolled in first-in-man trials. (4) Based on current Italian regulations, there is a need for a national register to monitor the participation of healthy subjects in different early clinical trials at the same or different centres for drug experimentation. (5) In view of a “new era of early phase trials,” the national legislation should offer Italian investigators conducting phase 0 and phase I trials a comprehensive guideline encompassing all principles sanctioned.The Drug approvals in the US, Europe & India are the most demanding in the world. The

primary purpose of the rules governing medicinal products in US, Europe & India is to safeguard public health. It is the role of public regulatory authorities to ensure that pharmaceutical companies comply with regulations. There are legislations that require drugs to be developed, tested, trailed, and manufactured in accordance to the guidelines so that they are safe and patient's well - being is protected.

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