

Clinical Research: A Multifaceted Discipline

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ABSTRACT

Clinical trial is a prospective biomedical or behavioral research study in human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices). The results from clinical trials determine whether the new drugs and treatment modalities are safe and effective; and if they can get a regulatory approval to be marketed. Clinical trials are multifaceted and include many disciplines - Regulatory, Ethics, Science, Economics, Agreements. The success of clinical trial rests on understanding responsibility, working in collaboration and practicing honesty.

Keywords: Clinical research, clinical trials, Good clinical practice, approval of new drugs.

Abbreviation: National Institute of Health (NIH), Central Drugs Standard Control Organization (CDSCO), Drugs Controller General of India (DCGI), European Medicines Agency (EMA), International Conference on Harmonisation (ICH), Good Clinical Practice (GCP), The Declaration of Helsinki (DOH), World Health Organization (WHO), Informed Consent Form (ICF), Ethics Committee (EC), Serious Adverse Event (SAE).

Introduction

The National Institute of Health (NIH) defines clinical research as research that directly involves a particular person or group of people or that uses materials from humans, such as their behavior or samples of their tissue [1].

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Clinical research [1] includes:

1. Patient-oriented research- Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are *in vitro* studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes:
 - a. Mechanisms of human disease, Therapeutic interventions,
 - b. Clinical trials, or
 - c. Development of new technologies.
2. Epidemiologic and behavioral studies
3. Outcomes research and health services research.

Clinical trial, one of the most common types of clinical research, is a prospective biomedical or behavioral research study of human subjects that

is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices) [1]. Clinical trials are used to determine whether new biomedical or behavioral interventions are safe and effective.

Clinical trials cover diverse disciplines – regulations, science, ethics, and commerce. These could be described by expanding each letter of the term RESEARCH as follows:

- **R**egulatory
- **E**thics
- **S**cience
- **E**conomics
- **A**greements
- **R**esponsibility
- **C**ollaboration
- **H**onesty

Regulations

Clinical trials are conducted as per national and international regulations.

In India, Drugs and Cosmetics Act 1940, Schedule Y and Indian Good Clinical Practice form the basis of regulatory framework, which need to be followed while conducting a clinical trial in India. The Central Drugs Standard Control Organization (CDSCO) headed by Drugs Controller General of India (DCGI) is the regulating body which is responsible for approval of New Drugs and Clinical Trials in the country [2].

Schedule Y describes Requirements and Guidelines for Permission to Import and / or Manufacture of New Drugs for Sale or to Undertake Clinical Trials [3]. The Schedule Y regulations are amended, as required, to meet the advances in scientific, ethical and pharmaceutical disciplines.

At present, most Indian clinical trials are a part of global trials of new therapies or are trials to meet regulatory requirements for export of new generic therapies. Thus these clinical trials in India would require compliance with requirements of international regulatory agencies such as United States Food and Drug

administration [4], European Medicines Agency (EMA) [5].

International Conference on Harmonisation (ICH) [6] Technical Requirements for Registration of Pharmaceuticals for Human Use describes globally acceptable guidelines for assessing efficacy, safety, and quality of drugs.

Ethics

A clinical trial is an experimental study in human beings. Hence, ethical conduct ensuring protection of rights, safety and well being of the participants is at the heart of clinical trial. The current standard for such compliance is good clinical practice (GCP).

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected and that the clinical trial data is credible [7].

The GCP guidelines – both Indian and ICH – have evolved from ethical guidelines such as The Nuremberg code, The Declaration of Helsinki (DOH), World Health Organization (WHO), The Belmont Report, and Indian Council of Medical Research Ethical Guidelines for Biomedical Research on Human Subjects [8]. The guidelines stress on the need to respect autonomy of the clinical trial participants, to maximize benefits and reduce risk to the participants. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society [7].

The clinical trial project proposal, the protocol, the informed consent form (ICF) should be approved by an ethics committee (EC) before the initiation of the clinical trial.

The EC is an independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public

assurance of that protection. The EC fulfills this responsibility primarily by, reviewing and approving / providing favorable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. The EC has to monitor the compliance to regulations and ethical guidelines throughout the conduct of clinical trial [7].

Another important aspect of ethical conduct of trials is the consent process.

Informed Consent is defined as 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 [7]. Freely given informed consent should be obtained from every subject prior to clinical trial participation.

Science

The clinical research is an experiment which should be scientifically sound. A clear, detailed protocol forms the backbone of the scientific conduct of a clinical trial.

ICH-GCP defines Protocol as a document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents [7].

The scientific background and the rationale should validate the need of developing a new drug or treatment modality and conducting the trial. A clinical trial cannot be justified ethically unless it is capable of producing scientifically reliable results. The protocol should describe the study hypothesis, objectives, efficacy and safety endpoints, methodology of conducting the trial and statistical analyses to establish the hypothesis. The study design has to generate statistically and scientifically sound answers to the hypothesis without undermining the safety of the study participants.

Economics

Clinical trial of a new drug is an expensive proposition, as it spans across many countries, includes hundreds of investigators, industry professionals and enrolls thousands of clinical trial participants. Hence management of budget becomes quite important.

The financial aspects require consideration of budget for the investigator, the institution, the infrastructure, the equipment, the lab testing etc

A major consideration in budget for clinical trial participants is compensation for participation, and medical management and financial compensation in case of serious adverse event (SAE) of clinical trial related injury or death.

The budget will include insurance or indemnification for such serious eventualities.

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

Agreement

The GCP guidelines require that the sponsor should obtain the Investigator's/institution's agreement [7]:

- (a) To conduct the trial in compliance with GCP, with the applicable regulatory requirement(s), and with the protocol agreed to by the sponsor and given approval/favorable opinion by the EC
- (b) To comply with procedures for data recording/reporting
- (c) To permit monitoring, auditing, and inspection
- (d) To retain the essential documents that should be in the investigator/institution files until the sponsor informs the investigator/institution these documents are no longer needed.

Other important legal issues are guarding confidentiality of the personal information of clinical trial participants, and the proprietary information of the company.

All these issues have to be documented in a legal agreement between main stakeholders – the sponsor companies and the investigators.

Responsibility

The regulatory and ethical guidelines stress on the responsibility of all stakeholders.

The professional and moral responsibility, for the due observance of all the principles, regulations and guidelines rests on all those directly or indirectly connected with the clinical trial including the researchers, those responsible for funding or contributing to the funding of the research e.g. industry sponsor, and the institution or institutions where the research is conducted.

The ethics committee's primary responsibility is to safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects [7]. Investigator is the person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team. The investigator(s) should be qualified by education, training, and experience to assume the responsibility for the proper conduct of the trial in compliance with regulations, GCP and the study protocol. The investigator's prime responsibility is human protection - guarding the safety of the clinical trial participant and data integrity – accuracy and completeness of data [7].

The sponsor is responsible for overall implementation of quality assurance system to ensure that the trials are conducted in accordance to the protocol, GCP guidelines, applicable regulations and Standard Operating Procedures.

Collaboration

There are many stakeholders involved in the clinical trial. The sponsor team consists of project managers, clinical research associates, regulatory professionals, medical monitors, data management, statistician, medical writers, auditors, etc. The Investigator team at site consists of principal investigator, co-investigator, clinical research coordinator, pharmacists, and nurses.

These teams located globally, manage diverse clinical trial processes. Hence, clear communication and distinct assignment of roles to all the members is of utmost importance to

complete the clinical trial successfully. Team work and collaboration are critical to achieve the key objectives of completing the clinical trial in time, within the budgeted cost and matching the quality requirements.

Honesty

The conduct of clinical trial should be in compliance with the principles of accountability and transparency whereby the research or experiment will be conducted in a fair, honest, impartial and transparent manner.

The clinical trial has to meet the quality standards for designing, conducting, recording, and reporting trials that involve the participation of human subjects. The scientific integrity of the trial, the credibility of the data from the trial, and ethical requirement of protecting rights, safety and well-being of trial subjects are the foundation on which the quality of a clinical trial rests.

Plagiarism or falsification of data and authorship are important ethical issues in publications [8]. The term 'misconduct in research' means fabrication, falsification, plagiarism, selective omission of data and claiming that some data are missing, ignoring outliers without declaring it, not reporting data on side effects/ adverse reactions in a clinical trial, publication of post-hoc analysis without declaring it, gift authorship, not citing others' work, not disclosing conflict of interest, redundant publication, and failure to adequately review existing research. It is essential that scientific objectivity is maintained with honesty and impartiality, both in the design and conduct of the clinical trial and in presenting and interpreting findings.

Conclusion

Clinical trial is a complex project which requires consideration of diverse regulatory, scientific, ethical, legal and commercial aspects. It is essential for a clinical research professional to understand these multiple facets to manage the project successfully.

Conflict of interest:

The authors disclose no conflicts of interest.

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