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REGULATORY REQUIREMENTS NECESSARY FOR CONDUCTING CLINICAL TRIAL IN INDIA: ACADEMICIANS MUST KNOW

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ABSTRACT

Different approaches used by the various national regulatory bodies led to lack of harmonization in the medical device industries. This article explains the method, beginning with standards adopted and acknowledged in various regulatory systems by the International Organization for Standardization (ISO). Manufacturers will familiarize themselves with the updated standard list and provide correct certificates of adherence as part of their registration process to ensure compliance with those requirements. Regulatory bodies in different countries make changes, from time to time, to their set of approved criteria used in the medical device regulatory process. Although the software and emerging technology are increasingly becoming common elements in medical devices, vendors now have to ensure compliance with more existing specifications. Such principles are international norms, which ensure they extend to the globe. Consequently, they could be embraced by any given region or country, perhaps with modifications or limitations. Generally, international standards are denoted with three sections. First, the issuing organization; second, a number; and third, the problem year.

INTRODUCTION

The academicians perform multiple functions research and administration, teaching and patient care. Good research finally provides evidence-based medicine and gives improve and better patient care with promoting health as ultimate goal. Research is however time-consuming, laborious, intensive task that takes several months to years to gain fruitful results. Research and drug development is too long and results in new drugs costing USD 1.78 billion on an average and approximately takes 13.5 years to discover and market. Pharmaceutical industry provides financial support for research and drug development including Phase I to Phase IV studies (human testing). These clinical trials studies are conducted by academicians as principal investigator in academic centres. The country's regulatory policy and requirements must be fulfilled because it is been funded by the pharmaceutical industry. Academicians carry out the initials studies known as 'Investigator Initiated Studies' (IISs). In this case the academician

provides the fund for the study possibly with the help of pharmaceutical industry. In IISs, the academician is responsible of sponsor and investigator and hence he is in-charge of ensuring the regulatory compliance in their research work.[1,2,3]

METHODOLOGY

The information related to the above mentioned title was gathered through various search engines such as Science Direct, Google Scholar and many more. Online books have also served as an excellent source of information. Documents and information's collected using numerous regulatory websites.

After collecting the information, the data was compiled according to the objectives.

DISCCUSSION

The National Regulatory Body (NRA) – The Central Drugs Standard Control Organisation (CDSCO) and the Drugs Controller General Of India (DCGI): NRA of India – CDSCO. Like CDSCO other Regulatory Body are US-FDA, European Medicines Agency and Health Canada. The Ministry of Health and Family Welfare (MHFW) is the body of India's Government in which CDSCO plays the role of its arm.

Mission of CDSCO. To enhance and safeguard people health in result to assurance of safety, quality and efficacy of drugs, medical devices and cosmetics.[4] Under CDSCO, the Drugs Controller General of India (DCGI) plays the major role for regulatory authority in clinical trial approval. The tasks include for DCGI are inspecting clinical research & manufacturing facilities of sponsor, inspecting trial sites and handle the roles and responsibilities of Central Drugs Testing Laboratory and the Regional Drugs testing Laboratory.

The Department of Health Research and the Indian Council of Medical Research: The ICMR is the main body responsible for coordination, promotion and formulation biomedical study. Department of Health Research and MHFW provide funds for the study.[5]

Key Documents in Clinical Research: Drugs and Cosmetics Act (1940) and Drugs and Cosmetics Rules (1945). In 1940, the Act came into force and regulates the manufacture, distribution and import of drugs in India and includes ensuring cosmetics and drugs commercialized in India are effective, conform and safe to critical quality standards. The act includes Rules, Chapters and Schedules which are amended time to time so as to maintain greater efficacy, safety and quality. The part of D&C Act which governs Clinical Research is Schedule Y (rules 122DA, 122A, 122DAC, 122B, 122E and 122D).[6,7] It is important that every clinical study that comes under the field of Schedule Y must comply with essential requirements. Schedule Y has 12 appendices, informed consent.

Ethical Guidelines of the Indian Council of Medical Research (2006): Revised Guidelines for ICMR released in 2017 - Ethical Guidelines for Biomedical Research on Human Participants.

These guidelines covers behavioural science research, biomedical and social study for health involving human volunteers and their data (biological) conducted in India.

Indian Good Clinical Practice Guideline (2001): A good clinical practice (GCP) guideline was released in 2001 by the CDSCO that attempted to be India specific, but unlike the ICH GCP guideline, has not been revised since.[8,9]

Regulatory Changes in India's Landscape (2005–2016): The Schedule Y amendment released on 20th January, 2005 saw dramatic changes that attempted to bring India on par with internationally prevalent regulations.[7] Some of the key changes included the definition of a clinical trial, permitting trials in India to be conducted in the same phase of drug development as elsewhere in the world, demarcation of clear roles and responsibilities of the sponsor, investigator and ECs, underscoring the importance of informed consent, requirement for studies in special populations and mandating that protocol amendments need approval from the office of the DCGI.[10]

Regulatory Requirements for the Conduct of Clinical Trials in India - What the Indian Researcher Must Know

A - Regulatory definitions. What is a 'clinical trial'?[11] It is defined as the systematic evaluation study of medicines or medical devices on human subject(s) to generate data for discovering and/or verifying:

- With the objective of determining safety and/or efficacy of the new drug
- And/or adverse effects
- The clinical pharmacological (pharmacodynamic and pharmacokinetic) effects

What is a 'new drug' A 'new' drug[12] is one: That has not been used to a significant extent in the country. An already approved drug that is now proposed to be used in a different dosage, different dosage form, a new route or a new indication. An example of this would be the intrathecal or epidural route of use of dexmedetomidine. Approved for use but has been on the market for <4 years after approval. A fixed-dose combination of two or more drugs, were approved earlier individually for certain claims, which are now proposed to be used in combination for the first time in a fixed ratio. All vaccines, Drugs made using the recombinant DNA technology

B - Conduct of the clinical trial: Conduct of the clinical trial. Clinical Trial is conducted under the supervision of the investigator and must ensure that trials are led as per the rules below:[13] In compliance with an EC and a DCGI approved protocol

In the case of IISs with 'new drugs', DCGI approval is no longer needed; only an EC approval is required - 16th March, 2016 G.S.R. 313 (E)[14] In compliance with GCP guidelines. All applicable regulations

Registration of Ethics Committees that approve studies (Rule 122DD): Investigators and Administrators of Academic Institutes should ensure that their Institutional Ethics Committees (IECs) are registered with the central licensing authority and the registration renewed at the end of 3 years.[15] This is mandatory for Regulatory Clinical Trials

Approval from Institutional Ethics Committee: All clinical trials need to have approval from the IEC. A recent regulatory reform to IISs will ensure that academics conducting 'New Drug' trials are no longer subject to DCGI approval and IEC approval. Such studies are not intended to produce data for the purpose of submitting regulatory proposals. In the event the IEC determines that the academic and regulatory goals of the trial could theoretically overlap, the office of the DCGI should be informed. When within 30 days the IEC does not hear from DCGI, the licensing authority is not allowed to grant permission. Understand the three forms of analysis carried out by the Committee on Institutional Ethics and the scope of the proposed work in each review group. The Ethics Boards work according to regular [SOPS] operating procedures, which typically are available on their web pages. Two wide categories of projects are generally reviewed by both the Full Board or Complete Committee Review [for all projects with a higher risk] and the Accelerated Review [for projects with a low risk; such as leaving clinical samples]. The work on public domain data, such as systematic reviews or meta-analysis, may also be "exempted from scrutiny." Researchers submitting proposals to the IEC should know the IEC SOPs and recognize the group in which their study / study applies and the scope of its evaluation.

Registration of the clinical trial with the Clinical Trials Registry of India: The CTRI is a private, electronic portal for the registration of researchers and regulatory studies. The registration of all studies on a public database is recommended. Registration in CTRI is, however, compulsory for regulatory clinical trials since June 2009.[16,17] Registration must be rendered before the registration of the first individual. Registration is critical from a publication point of view as publishers in many biomedical journals do not accept documents with intervening studies which are not registered with the Registry of Clinical Trials.

Obtain informed consent from participants: Researchers must ensure that all participants in a clinical trial receive written, informed consent. In addition, investigators are responsible for auditory recording the informed consent process (gazette notice dated 19 November 2013) for studies involving disadvantaged subjects (such as children or mentally impaired patients) and involving a new chemical entity or a new molecular entity.[18]

Report serious adverse events that occur during a clinical trial: A SAE is described as a clinical incident associated with death, patient hospitalization (if the study was performed in an outpatient manner), hospitalisations (if the study was performed in the patient), permanent

or significant impairments, or disabilities, congenital anomalies or birth defects, or otherwise life threatening or otherwise life-threatening conditions.[19] The timelines for reporting SAEs are given below:

- The researchers will report all SEAs to the DCGI, the sponsor and the IEC within 24 hours after their occurrence (they should only be reported to the IEC within 24 hours for academic studies).[20]
- If this cannot be achieved, the DCGI should be made aware of the reason for the late reporting of the SAE and the study
- Upon careful review, send SAE report to DCGI. Therefore, send it to the President of the IEC and the head of the organization where the trial took place within 14 calendar days of the incident.
- IEC will, after proper analysis, apply its report on the SAE and its opinion on the (if any) financial compensation to be paid by the sponsor or the sponsor and the DCGI within 30 calendar days of the incident.

Understand that compensation for death and injury related to the trial are now needed, and the effects of compensation particularly when university trials of 'new drugs' are performed. For a clinical test, insurance is appropriate, both when there is death and when a clinical trial injury occurs. The compensation formulas for both are described below:[21]

- ***Compensation for death****:* B × F × R/99.37, where 'B' is a base amount of 8 lakhs, 'F' is a age factor based on the Workmen Compensation Act and 'R' a risk factor that takes into account the severity, duration of disease and co-morbidities
- ***Compensation for permanent disability****:* (C × D × 90)/(100 × 100), where 'C' is the quantum of compensation which would have been given to the nominee in case of death of the participant and 'D' is the percentage disability suffered by the subject
- ***Compensation for an SAE leading to life-threatening disease:*** 2 × W × N, where 'W' is the minimum wage per day of the unskilled worker (in Delhi) and 'N' is the number of days of hospitalisation
- ***Compensation for birth defect or congenital anomaly****:* Medical treatment to be given as long as possible and the amount to be kept in a fixed deposit at a monthly rate equivalent to half the unqualified worker's minimum wage in Delhi.
- ***Addressing SAEs and compensation****:* Some organizations have a subcommittee of the SAEs (above and above the IEC) to study and evaluate SAEs on a regular basis. This should be a strong committee for institutes that do not have them. As both pharmaceutical and researchers-initiated (academic) studies may be possible with clinical trials, budget guidelines on the medical administration of side-effects (AEs) [SAEs] and on the provision of insurance for the participants in studies must be defined at institutional level.

Site preparedness (rule 122DAC): Understand that the regulator will still audit the site and can revoke the trial authorization and stop the analysis. Preparation of the study site must be assured at all times.

Studies with medical devices: The Ministry of Health and Family Welfare, Department of Health & Family Welfare, State Government of India [GSR 983 (E)] released a draft notification for medical devices [Medical Devices Rules 2016], of 17 October 2016. Medical devices are usually categorized by this notice as investigational medical devices and as medical devices licensed or approved. Chapter VII of this notification states that clinical trial with the former needs IEC and DCGI approval, while academic trials with the latter needs IEC approval only.[22]

Interventional anaesthesia trials are not "drug" trials. Study clinical trials – begun and include procedures such as intervention [e.g. comparison of the effectiveness of two separate brachial plexus block techniques] involves the approval and registration of the Institutional Ethics Committee.

Sources of funding for Academic Investigator Initiated Research: Several government and non-governmental organizations throughout the country finance

academic work and the researcher must submit on their home pages in request formats and timelines. Among them are: the ICMR, Biotechnology Department, Science and Technology Department and the Scientific and Industrial Research Council. However, the research investigator has also sponsored work by several pharmaceutical companies in the region. Industry financing may be given by supplies of medicines or monetary assistance or both. The research is guided exclusively by the investigator during these studies including its design, conduct and review and a clear understanding with the funders.

Working with a collaborator outside the country: The Health Minister's Screening Committee, a commission which works out of ICMR and meets quarterly for joint evaluation of these projects, needs more approval for studies involving employees from elsewhere.[23]

THE ROAD AHEAD:

India accounts for 17% of the world's population and 20% of the global burden of disease measured as disability-adjusted life-years. The national area for clinical research is therefore massive, because it faces both communicable and not transmissible diseases with a dual burden. A recent research found that the regulatory studies carried out in the country do not suit their health needs. The researchers should understand both the burden of the disease and the regulatory requirements a lot to alleviate the burden and suffering related to the disease in the world.[24, 25,26]

CONCLUSIONS

The clinical researcher must be read, understand, and follow the rules speedily and work together for the greater ment of the patient with the pharmaceutical industry. ECs must now be seen and understood – Gain and motivate themselves by repeated training and the use of standard operating procedures, as the consistency of the IEC examination is known to be variable across the world.[27] Finally, by allowing IECs to be allowed, by a regulation authority, to approve 'new' medicinal products without regulatory approval, the frameworks for greater security, evaluation and analysis of SAEs and budget arrangements for the insurance and reimbursement of those involved in those studies should be in place for researchers, IECs and institutional managers.

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