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INTRODUCTION

Medical science has advanced tremendously over the years. Newer, better and effective drugs are frequently being introduced to fight the ever-increasing list of prevailing and newly discovered diseases. Interestingly, every new drug that floods the market has to undergo a series of tests and a considerable study,[1] known as clinical trial, before it is actually manufactured for use by the population at large. Clinical trials prove to be a useful way for testing the efficacy and suitability of a drug. Carefully designed and well-conducted clinical studies have the potential to yield favorable results for the overall benefit of the society.

India has become a preferred clinical trial destination for several multi-national pharmaceutical companies. Notwithstanding its successful participation in many global clinical trials,[2] conducting clinical trials in India is still a matter of concern due to several reasons. This newsletter briefly analyses the basis of this concern, the regulations on clinical trials in India, and the shortcomings in the present system.

1.0 Regulatory framework

The principal legislation governing clinical trials, inter alia, is the Drugs and Cosmetics Act, 1940 (**"Act"**) and the principal authority is the Drugs Controller General of India (**"DCGI"**). Schedule Y (**"Schedule Y"**) to the Drugs and Cosmetics Rules, 1945 (**"Rules"**) stipulates the regulations for importing and/or manufacturing new drugs for sale and to undertake clinical trials in India.

Additionally, the Indian Council of Medical Research (**"ICMR"**) has issued Ethical Guidelines for Biomedical Research on Human Participants and Central Drugs Standard Control Organization has formulated Good Clinical Practices Guidelines (**"GCP Guidelines"**) in line with the international guidelines issued by World Health Organization and International Committee on Harmonization (**"ICH-GCP"**), which provide operative guidelines for ethical and scientific standards for the designing of a clinical trial protocol[3] including conduct, recording, safety and reporting procedures. It is compulsory for every company undertaking a clinical trial in India to strictly adhere to these guidelines.

While Schedule Y describes the procedure in terms of the application process for commencing clinical trials in India, the responsibilities of the sponsor, investigator and Ethics Committee (**"EC"**) in brief, the GCP Guidelines is more elaborately drafted. However, the regulations are overlapping and sometimes ambiguous and, consequently, impact the participants in a clinical study.

The following sub-sections briefly discuss provisions of Schedule Y and the GCP Guidelines. It further tries to analyze the loopholes and the ambiguous regulations that the authorities should perhaps take note of.

1.1 Schedule Y

Clinical trial on a new drug requires permission from the DCGI and the respective Ethics

[1] Before launching a drug, every pharmaceutical company undertakes pre-clinical trials (tests on animals), Phase I, II, III and IV trials on human beings.

[2] Drug called Tegaserod by Novartis, Voriconazole by Pfizer to name a few.

[3] It is a document that states the background, objectives, rationale, design, methodology and statistical considerations of the study.

Committee (**"EC"**) of the trial site.[4] The documents fundamental to the study, which contain the study procedure, details, instructions for conducting clinical trial namely the protocol, case record form, study subject's informed consent form, investigator's undertaking, has to be approved by the DCGI and the EC before commencing the study. The clinical trial process is spread over four phases in humans-

i. Phase I (Non therapeutic) trials, which mark the start of the process, are done for estimation of safety and tolerability of the new drug in a small population of healthy humans to determine the drug's tolerability, absorption, distribution, metabolism, and toxicity.

ii. Phase II (Therapeutic Exploratory) trials are done to evaluate the effectiveness of the drug for particular indications in patients with the condition under study, and to determine the common short-term effects and risk associated with the drug.

iii. Phase III (Therapeutic confirmatory) trials are done on larger populations of afflicted patients, in different stages of disease, to confirm the information gathered in Phase II and to compare the drug's effectiveness with an existing drug, if any, in the market.

iv. Phase IV (Post marketing) trials are done once the drug is approved to check the safety issues and other effects, if any.

Based on the existing rules, Phase I clinical trial on drugs discovered outside India is allowed only upon submission of Phase I results of other countries to the DCGI. Further, Phase II and III trials are permitted only after similar trials have been approved by regulatory authorities of the countries where such drugs have been developed. Thereafter, repeat Phase I trial is allowed with the prior permission of the DCGI.

Given the varying genetic profiles of people in different parts of the world, the health needs and requirements, the regulations should be amended to allow Phase I clinical trials to be done on Indians concurrently with global trials. This will enable a better assessment of the drug on Indians, their health and genetic profiles. Moreover, considering that India is emerging as an important place for conducting clinical trials, the amendment will bring India more in line with global studies and will act as an incentive to pharmaceutical companies. However, this will also call for stricter regulations and effective implementation thereof to prevent exploitation of Indians by multi-nationals.

1.2 GCP Guidelines

In addition to Schedule Y, the GCP Guidelines[5] serve as the guiding document for conducting clinical trials in India. It lists the procedures, practices, and methods to be adopted to ensure compliance with the international guidelines on clinical studies. However, there is still a level of ambiguity and lack of comprehensiveness as will be evident from the succeeding section. In any clinical trial, the key participants are:

- Sponsor - The company, individual or institution which initiates, manages and/or finances the clinical study.

- Site - The hospital where the study is conducted on subjects by the investigator.

- Investigator - A person who is responsible for the conduct of the study at the trial and the rights, welfare and health of the study subjects. Where a team of investigators are involved, the designated leader of the team, the Principal Investigator, has the responsibility to co-ordinate between all the investigators involved in the study at one site or different sites.

- Contract/Clinical Research Organization (**"CRO"**) - A CRO essentially performs all the tasks, duties, and obligations of the study. A written contract between the sponsor and the CRO defines the scope of responsibility of the CRO. In the absence of a specific responsibility or obligation in writing, the same is required to be assumed by the sponsor.

[4] Schedule Y, Rule 1. The prescribed application form is form 44.

[5] GCP Guidelines are issued by the Central Drugs Standard Control Organization (**"CDSCO"**) which functions under the Directorate General of Health Services formed by the Ministry of Health and Family Welfare.

- Study Subjects - An individual who participates in the clinical study. A study subject cannot be enrolled without obtaining a signed informed consent form.

In addition to the above, the EC or an independent review board of the site has an important role to play as it monitors the study and ensures compliance with the regulations throughout the duration of the study. Though GCP Guidelines are in line with the international practices on clinical trials, there are certain departures. For instance, guideline 4.8 indicates that completed subject identification code list should be in the sponsor's file. This is a potential violation of the subject's rights to confidentiality and privacy. Essential documents are needed for sponsor's independent audit function and inspection by the DCGI. The GCP Guidelines also lists essential documents for EC files. This suggests that the sponsor's auditor can review EC files. This is also not in line with ICH-GCP. It is important to eliminate such differences and bring the GCP Guidelines more in line with the globally applicable standards.

Further, it will be interesting to consider if the GCP Guidelines are enforceable in a court of law. By and large, Indian jurisprudence has confirmed that guidelines cannot be given effect to in a court of law.[6] All the key participants in a clinical trial have to comply with the GCP Guidelines. However, in the event of a default (non-compliance, serious adverse event, death of a subject), due to absence of the necessary legislative power under the GCP Guidelines, though it appears that the DCGI has wide powers, he can still not take any substantive action against the guilty. In such cases, the Act will prevail over the GCP Guidelines.

2.0 Loopholes in law and practice

Despite amending Schedule Y and introducing GCP Guidelines, clinical trials have invariably been in the spotlight for wrong reasons. Owing to the very nature of the study, i.e. involvement of humans as the object of study, law and ethics are bound to overlap. Therefore, it is understandable that drafting regulations to monitor these studies is not an easy task. But considering the number of trials that have been and are taking place in India, it is essential to remove ambiguities in the existing legislations, plug the gaps by introducing stringent laws to bring the guilty to books and ensure uniformity in the prevailing regulations. As of date, there are many loopholes in and abuses of the regulations. Some of them are discussed below:

1. The regulations are not categorical and are left to the reader's interpretation - For instance, rule 3 of Schedule Y (responsibility of investigator) states "Standard Operating Procedures (**"SOP"**) are required to be documented by the investigators for the tasks performed by them". It has not been elaborated further. It is not clear what the SOP should contain, in what manner and how they should be maintained, who shall maintain them, and who shall review and/or amend them. Similarly, it is not clear if the site is also required to maintain a SOP independent of the investigators. Whether the SOP will be a standard document meant for all the studies or will it be study-specific? The GCP Guidelines is also silent in these contexts. There needs to be greater clarity in this regard.

2. Lack of stringent punishment for defaulters - There is a definite lack of effective deterrence in the existing provisions. Several multi-nationals and local companies conduct trials in India. There have been many adverse events, reported mishaps, death of subjects, incorrect study procedures etc. but so far the DCGI has been unable to take any action against the guilty due to lack of stringent and speedy enforcement of the laws. Recent media reports[7] suggest that the Health Ministry, DCGI is planning to introduce ten years imprisonment for the persons found guilty of an offence in a clinical study. However, till the law is implemented, there is no protection for the subjects who actually suffer due to the adverse events that occur during such clinical studies.

3. Attribution of definite liability on the sponsor, CRO, the site, and investigator in case of a serious adverse event - In case of a foreign sponsor, the GCP Guidelines clearly state that it has to appoint a local representative or CRO and transfer any or all of the

[6] Exceptions being where a direction has been followed for long, if they confer a benefit upon individual etc.

[7] "Unethical clinical trials may invite painful penalty", Sushmi Dey, Economic Times dated April 15, 2009.

study related duties and functions but the ultimate responsibility for the quality and the integrity of the study data always resides with the sponsor.[8] The sponsor being the one who initiates the study, it is reasonable to place this responsibility. However, in cases of adverse events at sites, where the investigators and the sites are directly involved in conducting the study, it is unfair to hold the sponsor completely responsible. The liability and responsibility between the participants should be clearly demarcated and attributed proportionately.

4. Lack of an independent data safety monitoring board - There is no independent data safety monitoring board established by most of the clinical trial teams, hence adverse drug event or serious adverse events go unnoticed. Consequently, many subjects, who end up with adverse reactions or in some cases death, do not get their due in terms of compensation.

5. Lack of regular monitoring by the DCGI - The existing regulations require prior permission from the DCGI and EC for initiating the trial. However, once the trial is commenced, there is no check on the investigator sites or for that matter on the functioning of the ECs by the DCGI.[9] The regulations should have a mechanism to keep a tab on the trials, perhaps, a provision to the effect of appointing local boards in different areas to conduct surprise checks and visits to verify the documents, the methods adopted and the manner in which trials are conducted at the sites. In case of default, immediate and strict action should be taken against the guilty.

6. Process of selection of subjects by the sites - Every trial protocol has its own indusion and exclusion criteria in order to choose the subjects for the study. However, it has been observed that the economically weaker, illiterate sections of the society are sometimes exploited. In effect, it appears that many a times the selection criteria tend to be ignored and violated by the investigators and sites. And, these discrepancies come to light only in case of adverse events or due to media reports. It is imperative for the sites and investigators to perform the trials in an ethical manner and comply with the ICMR guidelines. The sites, investigators should be heavily penalized in cases of violation of selection criteria.

7. Lack of well-trained, professional investigators - A site involved in a clinical study engages many investigators and sub-investigators, who are principally the local doctors or junior doctors working in the hospitals. Lack of professional training, relevant experience, and knowledge can be disastrous for the subjects and the overall study. There should be a stringent mechanism for selecting, training, and appointing investigators in clinical trials. They should be well apprised with the legal regulations and ethical principles before induction in the study.

8. Role of Ethics Committee - In most of the cases, the committees are headed by the institutional heads, and follow their instructions rather than the EC's recommendations. At the central level, the central ethics committee at the ICMR issues guidelines but has no policing powers. The ECs should be monitored closely by a central agency or the central ethics committees should be given more powers to deal with the ECs at the sites.

CONCLUSION

One cannot deny the fact that clinical trial is the basis for introducing better drugs, medical practices, and devices. The fact that it involves law and ethics makes it a challenge for those framing the legal provisions. The Ministry of Health and the DCGI should leave no room for complacency when it comes to human trials and ensure that the loopholes are plugged by ensuring uniformity and removal of ambiguity from the existing regulations. However, law can regulate, monitor, and ensure protection of subjects only to a certain extent. Eventually, it is up to the proponents of clinical trial to adopt ethical principles/practices and not exploit or misuse fellow humans for commercial reasons. ***(Priyatha Rao)***

[8] Guideline 3.1.17.

[9] Though the ICMR has set up the Central Ethics Committee, greater monitoring is required.

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