Clinical trials and tribulations

Introduction

India has increasingly become a popular destination for conducting clinical trials for multi-national pharmaceutical companies. These companies test the efficacy and suitability of their drugs on Indian subjects before marketing them in India. Though the instances of clinical trials have been rising, the regulators have not been able to be up to the mark to keep a check on the irregularities in these clinical trials. Of late, clinical trials have been in news for all the wrong reasons and media is replete with news[1] of deaths due to severe adverse events (**"SAE"**) during clinical trial. It became official once a response was filed in the Parliament by the Minister of Health and Family Welfare stating that there have been 211 deaths due to serious adverse events in clinical trial in the past 6 months in 2012.[2] While clinical trials are required to adopt the fundamental ethical principle of ensuring the authenticity of biomedical data generated and the protection of subjects, these revelations raise serious concerns regarding the ethical practices followed during trials.

In light of the above finding the question of the malaise in drug regulations and its implementation has come up yet again. In this e-newsline, we shall try to examine the crucial elements of the existing and proposed regulations for conducting clinical trials and ascertain if there is a need to streamline the regulations or work on its strict enforcement.

1. Approval and Registration

1.1 *Approval*: Clinical trial on a new drug can be initiated only after the approval of the licensing authority and ethics committee has been procured. The ethics committee grants approval to the protocol prepared for conducting the trials. The proponents of clinical trials are expected to conduct the clinical trials in compliance with the approved protocol, the Good Clinical Practice Guidelines (**"GCP"**) issued by the Central Drugs Standard Control Organization (**"CDSCO"**), Ethical Guidelines for Biomedical Research issued by Indian Council of Medical Research (**"Ethical Guidelines"**), the approved protocol, and the schedule Y of the Drugs and Cosmetics Rules (**"DCR"**).[3] Effective December 21, 2011, the CDSCO issued a guidance document for industry on *"the Requirement of Chemical & Pharmaceutical Information including Stability Study Data before Approval of Clinical Trials/BE Studies."*

1.2 *Registration with CTRI*: A trial involving human participants, of any intervention such as drugs, surgical procedures, preventive measures, lifestyle modifications, devices, educational or behavioral treatment, rehabilitation strategies as well as trials being conducted in the purview of the Department of AYUSH is expected to register the trial in the Clinical Trials Registry of India (**"CTRI"**) before enrollment of the first participant. This step finds its genesis in the 2008 revised declaration of Helsinki at the general assembly of World Medical Association, which specifies that *"Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject."* This

[1] Please see http://www.thesundayindian.com/en/story/horror-of-clinical-trials-/22/16185/ and http://www.pharmalot.com/2012/07/clinical-trial-deaths-in-india-dropped-but/ (last visited on August 22, 2012)
[2] As covered in http://articles.timesofindia.indiatimes.com/2012-08-18 (last visited on August 22, 2012)
[3] For details on the regulatory aspect please see http://www.psalegal.com/pdf/E%20Newsline%20April%202009.pdf (last visited on August 22, 2012)

compelled the Drugs Controller General of India (**"DCGI"**) to make registration of clinical trials with the CTRI mandatory with effect from June 15, 2009.

The registration with CTRI involves public declaration and identification of trial investigators, sponsors, interventions, patient population, etc before the enrollment of the first patient. In addition, it requires submission of ethics approval and DCGI approval, if applicable. After a trial is registered, it is mandatory to regularly update the trial status or other aspects, which is made available for public display.

1.3 *Registration of ethics committee*: In addition to the registration of the trial, the CDSCO has now proposed to make the registration of ethics committees with the licensing authority mandatory in India. The licensing authority may grant registration in compliance with Schedule Y, the GCP and other applicable regulatory requirements for safeguarding rights, safety and well being of the trial subjects. If the licensing authority is not satisfied, it can reject the application with reasons and specify the conditions which must be satisfied before the registration can be granted. Thereupon, if the ethics committee fails to comply with any of the conditions of registration, the licensing authority may after giving an opportunity to show-cause, suspend or cancel the registration of the ethics committee for such period considered necessary. The registration shall be valid for a period of 5 years from the date of issue, unless not cancelled or suspended before. In 2011, the Drug Technical Advisory Board had come up with this suggestion in the wake of widespread complaints that the ethics committees at most of the clinical trial sites are not independent. Most of the ethics committees are active with no monitoring of the trials by the authorities. Once this comes into effect, this will add legitimacy to the "independence" of the ethics committee.

2. Recruitment of Subjects

2.1 *Procuring Informed Consent*: Schedule Y of DCR provides that while recruiting subjects for clinical trial, it is crucial to procure a freely given, informed, written consent from each study subject. The investigator has the obligation to provide information about the study orally as well as using a patient information sheet in a language that the subjects can easily understand. Where a subject is not able to provide informed consent (*unconscious person, minor, mental patient, etc*), the consent can be obtained from its legal representative, who can be the guardian of the subject or a relative or someone who can give consent on behalf of the subject. In case of illiterate subjects/legal representatives, an impartial witness should be present during the entire informed consent process to explain the same to the subject and/or legal representative and also, append signatures to the consent form. The patient information sheet, informed consent form, deviation to protocol, change in recruitment process, adopting a new method of recruiting subjects, changing the number of subjects (*increase or decrease*) requires prior approval from the ethics committee and such information and approval thereof should also be furnished to the licensing authority.

2.2 *Reporting untoward events*: The other most crucial aspect related to the subjects is the clinical trial compensation that is payable in the event of any adverse event (**"AE"**) or SAE. Pursuant to Schedule Y, all unexpected SAEs have to be reported to CDSCO within 14 calendar days and there is no format for such reporting. With the intent to bring uniformity and completeness of data in the process of reporting SAEs, the CDSCO released draft guidelines dated May 11, 2011

for reporting SAEs. Pursuant to this draft, every report (*both initial as well as follow-up reports*) of unexpected SAEs should be submitted with a cover letter to CDSCO as per Schedule Y. The assessment report should clearly mention whether the SAE occurred is related or unrelated (*Situations like unlikely, possibly, suspected, doubtful etc. should not be used*) with the trial.

3. Compensation to Subjects

3.1 *The existing regulation*: Regulation 2.4.7 of the GCP states that *"Research subjects who suffer physical injury as a result of their participation in the clinical trial are entitled to financial or other assistance to compensate them equitably for any temporary or permanent impairment or disability subject to confirmation from the IEC (Independent Ethics Committee). In case of death, their dependents are entitled to material compensation."* GCP in regulation 2.4.7.1 further provides that it is the obligation of the sponsor to pay the compensation.

3.2 *Specific responsibilities proposed*: In an attempt to further strengthen the provisions related to compensating the victims of clinical trial, on November 18, 2011, amendment was proposed in the DCR to include provisions related to compensation in the event of AE or SAE during clinical trials. Specific responsibilities of sponsor(s), investigator(s) and ethics committee were inserted. Accordingly, the sponsor shall pay for the medical treatment of the injured subject and compensation for the injury or death and the investigator shall, among others, **(i)** provide details of the informed consent form to the subject, **(ii)** inform the subject or its legal heirs regarding its rights and process to claim compensation, **(iii)** request the ethics committee to review and recommend for payment of medical treatment in case of injury. In the event of an injury or death, the ethics committee shall review the SAE and recommend compensation.

3.3 *Quantum of compensation*: The CDSCO has come up with a guideline for determining quantum of financial compensation to be paid in case of AE or SAE in clinical trials. Presently, there is no specific provision under DCR for payment of compensation in case of clinical trial related injury or death of the subject. For assessing compensation in the case of trial related injury or death following parameters needs to taken into consideration: **(i)** Age of the deceased; **(ii)** Income of the deceased; **(iii)** Seriousness and severity of the disease, the subject was suffering at the time of his/her participation into the trial; and **(iv)** Percentage of permanent disability.

To determine the compensation in case of trial related death following formula should be used: C1 = A x B (1 – F/100). The various methods of reaching to the value of A (*ascertaining multiplier A factoring income*), B (*ascertaining multiplier B factoring age*) and F (*risk factor*) has been provided elaborately in the draft. Upon calculation of all the multipliers, the amount of compensation to be paid shall be determined by using following formula, (*where D is percentage disability caused to the subject due to clinical trial)*: C2 = A x B (1 – F/100) x D/100.

There was always a need for a simple and expeditious procedure for payment of compensation and criteria for determining the amount of financial/material compensation to be paid for AE/SAE. The above formula based compensation seems more apt than simple determination done by the ethics committee so far. The proposed draft rule 122 DAB in clause (1) and (2) provides that in case of AE/SAE, compensation can be provided as ethics committee recommends. By the time this amendment comes into effect, the guideline for compensation should be in place as well to help in implementing the amended rules.

4. Inspection of clinical trial site

In order to further streamline the clinical trials in India, the CDSCO has issued Drugs and Cosmetics (3rd Amendment) Rules, 2012 regarding the inspection of premises of clinical trial sites by the regulatory officials with or without prior notice. This will allow them to keep a check on the process followed during clinical trials. The new amendment provides that:

(i) The clinical trials should be conducted in compliance to the approved protocols, requirements of Schedule Y, GCP and other applicable regulations;
(ii) Approval of the ethics committee should be taken before initiating the study;
(iii) Ethical aspects of the trial should be followed as prescribed in Ethical Guidelines;
(iv) Clinical trial should be registered with the CTRI;
(v) Annual status report on the trials should be submitted to the licensing authority;
(vi) Any suspected unexpected serious adverse reaction should be communicated with 14 days to the licensing authority;
(vii) For study related death or injury, compensation or medical care should be provided;
(viii) The sponsor/CRO, investigators shall allow CDSCO officer who may be accompanied by an officer of the concerned State Drug Control Authority to enter, with or without prior notice, any premises of sponsor/CRO and clinical trial site to inspect, search, seize any record, data, document, books, investigational drugs etc. related to clinical trials and provide adequate replies to any queries raised by the inspecting authority in relation to the conduct of the trial; and
(ix) The premises of sponsor/clinical research organization and clinical trials shall be open to inspection by the officer of the CDSCO, who may be accompanied by an officer of the concerned state drug control authority to verify compliance.

Upon inspection, the CDSCO inspecting office may **(a)** issue warning letter giving details of deficiency; **(b)** recommend that the study may be rejected; **(c)** suspend/cancel the clinical trial permission; **(d)** restriction of an investigator/sponsor/CRO to conduct future trials. There was an urgent need for such a regulation providing more teeth to the regulator. It would be interesting to see how this will be implemented. Incidentally, on August 16, 2012, the Drugs Controller General, Dr. G. N. Singh issued a notice for all parties engaged in clinical trials asking them to strictly comply with the existing regulations and take sufficient care while dealing with the subjects (*protecting their rights, safety and well-being*).

Conclusion

The process of streamlining the regulations of clinical trials is commendable. However, mere enactment does not solve the problem. To overhaul the existing regulatory structure, it is crucial that the laws are efficiently implemented and regulators sincerely keep a vigil on such discharge by companies. With more clarity on the specific roles and liabilities of sponsor, investigator and ethics committee, and the clarity on subject compensation and quantum thereof, several loose ends have been tightened and now only crucial step that is left is to bring these guidelines into effect and implementing them with full force by the help of trained staff.

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