Compensation for Clinical Trial-Related Injury and Death in India

India was considered a preferred destination for the conduct of clinical trials, with pharmaceutical companies (both Indian as well as foreign) utilizing the 'Advantage India' factor (large, diverse and treatment-naive patient population, trained human resources, good clinical practice compliant investigators/sites, relatively low cost of conducting clinical trials as compared with the developed world) to the fullest [1]. However, isolated cases of alleged incorrectly conducted trials not conforming to the principles of ethics [2, 3], coupled with unbalanced media reporting have generated debate from public to parliament regarding clinical trials in the country [4]. Taking up this issue, a Non-Governmental Organization named Swasthya Adhikar Manch filed a Public Interest Litigation in the Supreme Court of India [5]. The prime concerns raised via this litigation pertained to the process of informed consent in clinical trials and justifiable compensation to trial participants for injury or death. An affidavit filed by the Government of India in response to orders by the Supreme Court revealed that, during the period between 2005 and 2012, a total of 2,868 clinical trial participants died, of which 89 deaths were considered to be related to trials [6]. Out of these, compensation was paid to the relatives of the deceased in 86 cases; while in three cases, the whereabouts of relatives could not be traced for payment of the compensation.

The amount of compensation paid ranged from 55,000 to 4,200,000 rupees and its assessment was not based on any objectively defined guidelines/formula, but was decided according to the best judgment of ethics committees and/or the sponsor/investigator. These incidents have led the patient community to believe that they were treated like guinea pigs and have created a negative atmosphere against clinical research in the country. The necessity of conducting clinical trials for better therapeutics has not been appreciated much by the public, patients, media or even policy makers. The issue gets compounded by a lack of awareness, regulations and the monitoring mechanism regarding compensation for trial-related injury and death [7]. The media plays a constructive role as a whistle blower, but often inadequately informed and unbalanced reporting has created an atmosphere that is not conducive for promotion of 'clinical research' in general and 'clinical trials' in particular in the country [8]. This became evident from the sharp drop in the number of clinical trials (from 529 in 2010 to 253 in 2012 to 107 in 2013) approved by Drug Controller General (India) [DCG(I)] [9], and in the number of new drugs (from 224 in 2010 to 35 in 2013) approved for marketing in India [10].

The Supreme Court took cognizance of this important issue and directed the government to formulate appropriate regulations and effective oversight mechanisms to ensure participants'

safety in clinical trials . In light of an order by the Supreme Court of India, the government has put in place a three-tier system for approval of a clinical trial along with several other measures by amending Drugs and Cosmetics Rules, 1945 to ensure the safety and welfare of trial participants. Three landmark amendments regarding the provision for compensation in clinical trial-related injury or death, conduct of clinical trials, and registration of independent ethics committees were notified by the Ministry of Health and Family Welfare on January 30, 2013; February 1, 2013 , and February 8, 2013], respectively. The issue of justifiable compensation to participants who suffered trial-related injury or death is accorded priority as it is viewed as one of the most important areas of clinical trials. The notification related to compensation inserted a new Rule 122-DAB and gave the definition of clinical trial-related injury or death for the purpose of paying financial compensation. The draft notification to further amend this rule was issued vide GSR 292(E), dated April 24, 2014

The rule states that any injury or death occurring due to any of the following reasons will be considered as clinical trial-related injury or death, as the case may be:

(a) Adverse effect of investigational product(s).

(b) Violation of the approved protocol, scientific misconduct or negligence by sponsor or its representative or the investigator.

(c) Failure of investigational product to provide intended therapeutic effect.

(d) Use of placebo in placebo-controlled trial.

(e) Adverse effect due to concomitant medication excluding standard care, necessitated as part of approved protocol.

(f) For injury to child in utero because of the participation of parent in clinical trial.

(g) Any clinical trial procedures involved in the study.

However, these amendments, though made with all good intentions, have generated much debate. Opinions

are being expressed on both sides of the argument regarding various aspects of the amendments. In this article, we have addressed some issues where more clarity will help in establishing confidence among various stakeholders, including the academic researchers.

Detailed deliberations of these issues on various platforms by involving all stakeholders will help in removing current ambiguities regarding interpretation of these regulations.

Although the patient is the ultimate beneficiary in clinical research activity, because of the unique socio-economic conditions in India (low literacy, poverty, general lack of medical facilities) and the unique doctor-patient relationship, the patient ends up being the most vulnerable in the clinical trial process. Of all the stakeholders, the patient community is the most disorganized and there are hardly any platforms for them to express views and concerns.

Therefore, to cover these vulnerabilities, the philosophy of ‘no-fault compensation’ is adopted for trial related
injury or death in India. Under this provision, every injured participant gets compensated, even if the injury was anticipated/expected and fully explained to the participant through the appropriate informed consent process. In other words, the trial participant or their kin need not prove it was anybody’s fault and need not approach a court of law to seek compensation for the injury or death occurring due to participation in a clinical trial. This system is generally perceived to be more predictable and efficient and provides consistent coverage to the trial participants in case of injury or death. This also increases the level of confidence in stakeholders towards clinical trials. In a few other countries (e.g., France, Spain, Belgium and the UK), the compensation for clinical trial-related injury is also provided on a nofault basis. As there is no compensation formula in these countries, the methods of determining the quantum of compensation vary widely from case to case. In the US, on the other hand, ‘Tort’s law’ is followed in which the compensation seeker has to prove in a court of law that
the trial-related injury has occurred due to the fault of either researcher or research procedure. Even free management of trial-related injury is not mandatory under federal laws in the US. In China, compensation is only applicable for injuries caused by defective quality of the investigational product. In other words, if the drug causing injury conforms to the applicable standards, then it is not ‘defective’ and the compensation is not applicable.

3 Compensation Provisions in India for Clinical Trials and all Clinical Research

The Gazette notification dated January 30, 2013 makes provision for ‘compensation for injury or death in case of clinical trial’ by making an amendment to the Drugs and Cosmetics Rules, 2013. The rule 122-DAA of the Drugs and Cosmetics Rules defines clinical trial as ‘‘a systematic study of new drug(s) in human subject(s) to generate data for discovering and/or verifying the clinical, pharmacological (including pharmacodynamic and pharmacokinetic) and/or adverse effects with the objective of determining safety and/or efficacy of the new drug’’. Clearly, the term ‘clinical trial’ under the rule pertains only to the study in human subjects(s) of unapproved drugs and new drug(s). It essentially does not cover or refer to other types of clinical research. According to Rule 122-E of the Drugs and Cosmetics Rules, 1945, ‘new drug’ includes any recently approved drug within a period of 4 years of its initial approval; a new fixed-dose combination of two or more drugs; and any drug that is now proposed to be marketed with modified or new claims, namely indications, dosage, dosage form (including sustained-release dosage form) and route of administration. The current rules for compensation pertains only to the ‘clinical trial’ as mentioned under Rule 122-DAA of the Drugs and Cosmetics Rules, 1945 and does not encompass other areas of clinical

research involving human subjects/patients such as epidemiological studies, non-interventional studies not involving any new drug, etc.

4 Issues in Assessment of Compensation

Some important issues around the rules for compensation in case of injury or death related to clinical trial are discussed below.

4.1 Adverse Effect of Investigational Product(s)

4.1.1 Adverse Event or Serious Adverse Event It is important to clarify that the rule of compensation applies to only those adverse events (AEs) that are required to be reported. As per the rules, all serious AEs (SAEs) are to be reported within a stipulated time frame. AE that do not fall into the SAE category are not required to be expeditiously reported and, therefore, do not fall under the clause of compensation. AEs other than SAEs are reported by the sponsor as part of the trial reports. This clarification is important because confusion may arise if the clause is read in isolation to mean that any AE caused due to use of the investigational product in a clinical trial needs to be compensated. The AEs in this context should be read and understood as SAEs and that not every AE falls under compensation rules.

4.1.2 Expectedness and Relatedness

The compensation for a clinical trial-related injury or death is to be paid even though the trial participant was fully informed about the possibility of its occurrence before the trial and the subject has signed the informed consent. However, the expectedness of an AE does not necessarily establish the causality with the drug. Even if it is a well-recognized AE of a drug, the causality in that particular case needs to be established. For example, if a trial participant taking carbamazepine suffers from severe skin reactions (a known AE of carbamazepine), resulting in prolongation of hospitalization, which is classified as an SAE, still, there is need for causality assessment as it could be due to other concurrent medications, underlying disease conditions, etc. If the AE is determined to be related to the trial irrespective of expectedness, then the sponsor is required to pay the compensation amount.

4.1.3 **Possible Scenario of a Second Serious Adverse Event (SAE) During Management of a Primary SAE**

An SAE can happen during appropriate management of a previous SAE which has occurred due to clinical trial intervention. The Association of the British Pharmaceutical Industry

(ABPI) recommends that any injury caused during management of an AE would be compensated as if it was caused by the investigational drug only [27]. To
cite an example, in a trial of monoclonal antibodies, if a trial participant develops tuberculosis due to reactivation of latent infection and the causality is established, the participant should be managed and compensated for tuberculosis. Subsequently during the course of antitubercular treatment, if the trial participant develops hepatitis due to anti-tubercular drugs and is hospitalized, the sponsor also needs to pay for management of the condition, since this new SAE (hepatitis) is the direct sequel of the initial SAE (tuberculosis). According to the recently issued advisory by the Indian regulator, compensation has to be paid even if the SAE was discerned after the trial was over, provided relatedness is established [28]. However, clarity needs to be evolved whether the trial participant is entitled to compensation for the hepatitis (second SAE) which occurred during treatment of tuberculosis (first SAE).

4.2 Violation of the Approved Protocol, Scientific Misconduct or Negligence by Sponsor or its Representative or Investigator

As per the present rule, if the subject suffers from any clinical trial-related injury or death which is due to protocol violation, or negligence of the investigator or of the supporting staff, compensation must be paid to the trial participant/nominee. It has to be emphasized here that the trial participant will be eligible for financial compensation and it will be separate or in addition to the criminal enquiry/action by the medical registration authority or the state in case of alleged scientific misconduct or negligence. However, once such negligence of the investigator leading to injury or death has been established, and compensation has been paid under the compensation rule, there is no further provision under the Drugs and Cosmetics Act, 1940 to take penal action against the investigator. This evidence may, however, be used by the affected party in a court of law when seeking criminal action, and also by the Medical Council of India (MCI) to take appropriate action under the MCI Act, including the cancellation of registration of the investigator [29]. Thus, in such scenarios, there are three authorities that will carry out action against the erring investigator-DCG(I) for payment of compensation, MCI, and a court for punitive action.

4.2.1 What Happens When a Trial Participant Violates the Protocol?

Trial-related injury might also occur due to protocol violation (intentional or unintentional) on the part of the trial participant. For example, a female of child-bearing age participates in a trial of category X (teratogenic) drug and is advised to use double contraception as part of the study protocol. According to current understanding, if such a participant becomes pregnant and the fetus has congenital malformations or death, compensation needs to be

paid to the participant. This pregnancy would have occurred due to participant negligence in the use of contraception and would not have taken place had the subject carefully followed the instructions of the investigator. It can also be retrospectively argued that the pregnancy occurred because the investigator was not able to fully convey the importance of contraception or the subject did not pay attention to what was written in fine print on the consent form. The mandatory audio-visual recording of the informed consent process can help in deciding such situations [30]. The situation gets further complicated when the participant claims that she had used appropriate contraceptive methods and the pregnancy occurred due to contraceptive failure. It is difficult to prove the culpability of either the participant or the investigator in causing this AE. In such a scenario, causality assessment becomes very difficult. The compensation has to be paid in these cases by giving the benefit of the doubt to the participant. However, the rule is silent in the case of clear-cut protocol deviation on the part of the trial participant and guidelines need to evolve to address this issue.

4.3 Failure of Investigational Product to Provide Intended Therapeutic Effect

The basis of a clinical trial is clinical equipoise in that the efficacy of the investigational product (trial drug) is not established, and it has equal chances of being efficacious or not exhibiting the desired and anticipated therapeutic benefit. Recently, Hay et al. [31] reported that in the US, the likelihood of getting marketing approval for a lead indication of new molecular entities entering a phase III trial was 68 %. Lack of efficacy (54 %) was the leading cause for suspension of these trials in the phase III stage, other reasons being safety (9 %), commercial (18 %) and unknown (19 %) [31]. Genetic polymorphisms can be one of the reasons for a drug being less/non-efficacious in certain subjects. The only certainty during the clinical trial is of uncertainty. Clinical trials are designed in such a manner that standard of care is not compromised; however, in certain situations the use of an investigational drug in place of standard of care may become desirable under close monitoring and adequate safeguards. Therefore, in these situations, if the trial participant, in spite of all possible safeguards, suffers from injury or death due to lack of intended therapeutic effect of the trial drug, such cases deserve compensation. Considering this logic, the Government of India has recently issued draft rules vide GSR 292 (E) dated April 24, 2014 to amend Rule 122-DAB and other compensation-related provisions . According to the draft rules, compensation is applicable if the trial related injury or death has been caused by ‘‘failure of investigational product to provide intended therapeutic benefit in case the standard care, though available, was not to be provided to the subject as per the clinical trial protocol’. It is expected that the final revised version will adequately address this issue.

4.4. Compensation in Clinical Trials Having Mortality as an Endpoint

In certain situations, such as patients with terminal cancer, the natural progression of the disease can itself lead to death despite standard of care being provided to the patient. Also, in trials with mortality as the end point, death may occur despite the trial drug proving to be efficacious. If mortality occurs in a participant who is being given a trial drug over and above the standard of care, the participant is not entitled to compensation. It needs to be understood that the compensation should be awarded only in cases where the life of the subject is cut short because of the investigational product and not because of the progression of the disease itself.

4.5 Use of Placebo in Placebo-Controlled Trials

The use of placebo is an important tool to evaluate the safety and efficacy of new drugs. It is widely used in clinical trials as an add-on to standard care to evaluate the investigational drug. However, the use of placebo in clinical trials in general is considered unethical if any standard treatment is available for that particular disease condition. The trial participant cannot be denied treatment because of enrolment in the placebo arm of the trial, as it may result in substantial and permanent harm. Placebo by itself is not intended to provide any therapeutic benefit. According to the existing regulations, a patient in the placebo arm of a trial shall be entitled to compensation for injury or death due to lack of intended therapeutic effect of the trial drug.

Even if the participant is withdrawn from the placebo group, compensation is applicable for the injury which might have already taken place due to withholding active intervention. Concerns have been raised by various stakeholders that all such trial participants, including those in whom placebo was used as an add-on to standard of care, may need to be compensated and that this may act as an inducement for participation in the trial. The amended clause, as mentioned in new draft rules, amply clarifies this matter: trial-related injury or death will be deemed to have occurred with ‘‘use of placebo in placebo-controlled trials in case the standard care, though available, was not to be provided to the subject as per the clinical trial protocol’’.

4.6 Adverse Effect due to Concomitant Medication, Excluding Standard Care, Necessitated as Part of Approved Protocol

A trial participant could be taking a number of other medications besides the test drug, which could give rise to adverse effects either due to their pharmacological properties or due to drug interactions. As per the regulations, if the adverse effect is caused by such concomitant medication, the trial participant will be entitled to compensation only if this concomitant

medication is not part of the standard care for that illness. The concomitant medication is taken as per protocol imperatives and hence it restricts the participant from taking other medicines, which may be of the same therapeutic class. Therefore, a SAE has occurred as a direct result of protocol requirements and hence compensation needs to be paid by the sponsor.

4.7 For Injury to a Child In Utero Because of a Parent's Participation in a Clinical Trial

According to the recently issued draft formula for determining the quantum of compensation in case of clinical trial-related injuries other than death, compensation will be applicable in cases of death or deformity to a fetus in utero resulting from participation of either or both of the parents in a clinical trial. However, causality assessment will be difficult in such cases and it may be misused.

4.8 Any Clinical Trial Procedures Involved in the Study

Clinical trials not only involve administration of a test drug but may also involve certain procedures like venipuncture, bone marrow aspiration, tissue biopsies, contrast imaging studies, etc. Such intervention procedures could also give rise to AEs such as nerve injury, sepsis, contrast nephropathy, etc. Compensating these injuries fulfils the laws of natural justice, since injury has happened only because of their participation in the clinical trial. For example, a participant in a clinical trial, who underwent a contrast-enhanced MRI as part of the study protocol, develops contrast-induced acute renal failure. Compensation is applicable in this case since this injury has happened due to a trial-related procedure.

5 Regulatory Challenges in Causality Assessment

Conventionally, there are three methods of causality assessment: (a) based on opinions and deliberations of experts; (b) based on algorithms such as the Naranjo scale; and (c) probabilistic approaches such as the World Health Organization Uppsala Monitoring Centre (WHO-UMC) scale. In classical pharmacovigilance, the most commonly used method is the WHO-UMC scale, in which the causality is classified as certain, probable, possible, and unlikely [32]. However, when performing causality assessment for assessment of compensation, this has to be decided as related or otherwise. The major challenge is how to decide relatedness with maximum objectivity. The issue of causality assessment becomes more complex because of possible variations in assessment at four levels: Investigator, sponsor, Independent Ethics Committee and Expert committee (constituted by the licensing authority). The final order regarding the compensation is issued by the licensing authority on the recommendations of Expert committee. Presently, this is being done after detailed

deliberations in each case. The comprehensive regulations for causality assessment in light of regulatory requirements will further improve the scientific rigor and objectivity of decisions regarding compensation in clinical trials.

6 Conclusions

The Government of India has recently introduced several regulations regarding compensation for clinical trial-related injury or death to ensure that participants' interest is safeguarded in clinical trials in India. The regulations have been made after detailed deliberations, consultations, and analysis of the situation. These steps were essential to fill the gaps in the regulations, in the absence of which there could be potential harm to trial participants, who are relatively less informed compared with their counterparts in the developed world. However, it is perceived that, on a few points, there is some overcorrection which needs to be adjusted based on evidence and detailed discussion with all stakeholders, so that the progress of science is also not affected. These regulations should be clearly understood and followed correctly by all the stakeholders. They should be implemented in letter and spirit, with a philosophy of maintaining a delicate balance between inherent risk in the scientific pursuit for patients' benefit and safety of the trial participants by virtue of their participation in clinical trials of these medicines. The regulatory guidelines are part of a dynamic process and will continue evolving as per the changing requirements and demands of the system. Therefore, these regulations must be carried forward by proactively responding to such challenges with suitable clarifications and/or amendments, without compromising the trial participants' well-being.

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