

# Compensation to clinical trial participants in India: A gap analysis

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## Abstract

The recent amendments notified by the Government of India, for conducting clinical trial, is greatly appreciable as promoting safety and well-being of human subjects. These rules clearly state that medical management of injuries in clinical trials is mandatory, and clinical trial-related injury or death needs to be compensated over and above the medical management. These rules need to be reconsidered for simplification and better understanding of issues regarding compensation. There is a need of clarity at some points which should be discussed with all stakeholders for better understanding of current regulations. In our view, attention must also be given to academic investigators, during discussion to promote availability of cost-effective treatment in India.

**Keywords:** Adverse event, ethics, injury/death

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## INTRODUCTION

In the year 2004, global clinical research industry focused toward India as “hub of clinical research” due to availability of large number of participants. Since then, policymakers of the Government of India have been trying to modify the rules, and regulatory aspects include adoption of recommended set of internationally recognized ethical and scientific quality requirements known as good clinical practice (GCP) to promote the clinical trials. The policy modifications in India attract various international Clinical Research Organizations (CROs) to expand their business of clinical research program. India hosts nearly a fifth of all global clinical trials with a huge potential for financial and scientific gains.<sup>[1,2]</sup> CROs are taking advantage of getting large pool of patients, highly skilled medical investigators,

lower drug development costs, and timely completion of clinical trials in India.<sup>[3-5]</sup> The reasons for low cost of drug development are cost-effective human resource, low recruitment cost, and lower rate of compensation for any injury sustained or death during the research process. In fact, CROs even recruit patients without any formal assurance of compensation because a large proportion of participants in India are illiterate and lured into trials by offers of free health care and financial inducements. The trial participants are not properly informed regarding the benefits/risk of treatment.<sup>[6]</sup>

The efforts of Indian government toward promoting clinical research were greatly appreciated but poor regulation guideline for research was a great matter of concern. This matter has already been highlighted by world

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media showing unethical clinical trials, where participants are not compensated properly for injury/death. The flaws in informed consent procedure and nonexistence of clear-cut guidelines for compensation are also becoming serious issue for trial participants.<sup>[7]</sup>

### ETHICAL PRINCIPLES AND PROVISION FOR COMPENSATION

The statement of compensation for clinical trial participants has been put forward clearly in the 2013 version of the “Declaration of Helsinki” adopted in 1964 by the World Medical Association which states that “appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.” This declaration is widely regarded as cornerstone document on human research ethics. The Indian law for clinical trials, i.e., the Schedule Y<sup>[8]</sup> 2005 had clearly stated that informed consent form (ICF) must include the compensation procedure as an essential part in the document. The Indian Council of Medical Research guidelines<sup>[9]</sup> as well as Indian GCP guidelines<sup>[10]</sup> advocate provision of compensation to trial participants for any kind of injury/temporary or permanent disability. In case of death, their dependents are entitled to material compensation. The Drug Controller General of India (DCGI)<sup>[11]</sup> has previously directed that the clause clearly mentioning that any trial injury or death and medical care will be compensated by sponsor must be included in ICFs.

In spite the presence of stringent rules to follow ethics, some cases reported violation of ethical principles<sup>[12]</sup> coupled with unbalanced media reporting which raised debated on this issue from public to parliament regarding the status of clinical trials in country.<sup>[13]</sup> In light of this issue, an NGO (Swasthya Adhikar Manch) files litigation in the Supreme Court of India.<sup>[14]</sup> The litigation raised an objection to informed consent procedure in clinical trials and compensation delivered to trial participants for injury and death. In India, by the year 2005–2012, there were a total of 2868 deaths of trial participants, out of which only 89 deaths were found to be related to trial.<sup>[15]</sup> Compensation was paid to 86 participants as relative of three participants could not be traced. The amount of compensation paid ranged from 55,000 to 4,200,000 rupees and its assessment was not based on any objectively defined guideline/formula but was decided according to the best judgment of Ethics Committees and/or the sponsor/investigator. The Supreme Court of India considering this issue directed the government to bring regulation and mechanism to ensure the safety of clinical trial participants.<sup>[16]</sup>

As per the order of court, government made a three-tier system for the approval of clinical trials and amended the Drugs and Cosmetics Rule 1945 to ensure the safety of participants. There were consecutively three gazette notifications by the Ministry of Health to put amendments for clinical trial-related injury and death, conduct of clinical trials, and registration of Ethics Committee on January 30, 2013, February 1, 2013, and February 8, 2013.<sup>[17-19]</sup> The provision of compensation was notified by inserting a new rule 122 DAB entitled, “Compensation in case of injury or death during clinical trial.” The Government of India recently issued a draft rule vide G.S.R 889 (E) dated December 12, 2014, to amend rule 122 DAB, subrule 1 of Drugs and Cosmetics Act 1945 that “in case of an injury occurring to the subject during the clinical trial, free medical management shall be given as long as required or till such time it is established that the injury is not related to the clinical trial, whichever is earlier.” Similar amended was also made in Schedule Y of Drugs and Cosmetics Act. In addition to this, notification also stated in subrule 2 (A) that “in case, there is no permanent injury, the quantum of compensation shall be commensurate with the nature of the non-permanent injury and loss of wages of the subject.” There was an amendment in subrule 5 clause IV of Schedule Y to state “Responsibility of Ethics Committee” that “in case of serious adverse event occurring to the clinical trial subject, the Ethics Committee shall forward its report on the serious adverse event, after due analysis, along with its opinion on the financial compensation, if any, to be paid by the Sponsor or his representative.”<sup>[20,21]</sup>

### QUANTUM OF COMPENSATION

The licensing authority is primary body for the causal assessment of injury/death and compensation amount to be paid for it to trial participant. In case of occurrence of serious adverse event (SAE), the Expert Committee communicates its recommendation about causality and quantum of compensation to the licensing authority, and then, the licensing authority shall pass the final order.<sup>[22]</sup> The sponsor needed to compensate the participant as per order of licensing authority. In case of failure to comply with the order, licensing authority may take necessary action as per rule, including suspension or cancellation of the clinical trial and/or restricting sponsor including his representative(s) to conduct any further clinical trials in India.

As per rule 122 DAB of Drugs and Cosmetics Rules 1945, this is the responsibility of the sponsor to compensate financially in case of clinical trial-related injury/death as per the order of DCGI based on recommendation of

Expert Committee. In case of SAE other than death, the cause of injury and amount to be given to participant is finalized by the DCGI as per the report submitted by Investigator, Sponsor, and Ethics Committee. A compensation formula has already been proposed by the Independent Expert Committee for clinical trial-related death which is as under.

$$\text{Compensation} = \frac{B \times F \times R}{99.37}$$

Where,

B = Base amount (i.e., 8 lakhs).

F = Factor depending on the age of the participant (based on Workmen's Compensation Act).

R = Risk factor depending on the seriousness and severity of the disease, presence of comorbidity, and duration of disease of the participant at the time of enrollment in the clinical trial between a scale of 0.5 and 4 as under:

- i. 0.50: Critically ill patient (expected survival not more than 6 months)
- ii. 1.0: High-risk patient (survival expected between 6 and 24 months)
- iii. 2.0: Moderate-risk patient
- iv. 3.0: Mild-risk patient
- v. 4.0: Healthy volunteers or participant of no risk.

However, in case of 90% expected mortality or more within 30 days, a fixed amount of Rs. 2 lakhs should be given.

In view of the above, a committee was constituted to work out a formula to be followed to determine the amount of compensation in case of clinical trial-related injury (other than death).

#### Serious adverse event causing permanent disability to the participant

The committee arrived at a conclusion that amount of compensation to be paid in case of 100% disability should be 80% of the compensation which would have been due for payment to the nominee(s) in case of death of the participant. The amount of compensation for disability which is <100% will be calculated based on the presence of actual percentage disability.

Accordingly, committee arrived at the following formula:

$$\text{Compensation} = \frac{D \times 80 \times C}{100 \times 100}$$

D = Disability percentage.

C = Compensation amount for payment to the participant's nominee(s) in case of death of the participant.

#### Serious adverse event causing congenital anomaly or birth defect

The committee opined that the compensation in such cases should be a lump-sum amount such that if that amount is kept by way of fixed deposit or alike, it should bring a monthly interest amount which is approximately equivalent to half of minimum wage of the unskilled worker (in Delhi). The committee noted that this aspect was duly considered while fixing Rs. 8 lakhs as base amount for determining the amount of compensation in case of SAE resulting into death. Hence, the committee decided that quantum of compensation in such cases of SAE should be half of the base amount as per formula for determining the compensation for SAE resulting into death.

#### Serious adverse event causing life-threatening disease

The committee arrived at the following formula.

$$\text{Compensation} = N \times W$$

Where,

N = Number of days for life-threatening situation requiring medical care, irrespective of days of hospitalization.

W = Minimum wage per day of the unskilled worker (in Delhi).

#### Reversible serious adverse event in case it is resolved

$$\text{Compensation} = 2 \times W \times N$$

Where,

W = Minimum wage per day of the unskilled worker (in Delhi).

N = Number of days of hospitalization.<sup>[22]</sup>

### ISSUES REGARDING COMPENSATION ASSESSMENT

The rules of G.S.R 53 (E) vide; Gazette notification by the Ministry of Health dated January 30, 2013 stated 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. Noncompliance of the approved protocol
- 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 procedure involved in the study.

In light of the above, the following issues require further analysis.

#### Adverse effect of investigational product(s)

Adverse event (AE) is a part of sponsored clinical trial report of individual participant while SAE is reported to licensing authority within timeline as per the direction of the regulatory agency and needs to be compensated. While deciding the compensation, these two terms shall be dealt separately and must be clarified as confusion may occur if read in isolation.

Causality assessment is crucial and important part of trial and thus requires expertise to assess the expectedness and relatedness as the compensation is to be paid even when participant was informed about the expectedness of AE and given a written informed consent. Relatedness of AE cannot be ensured due to concomitant medication and underlying disease condition.

Occurrence of second SAE during the management of primary SAE is another critical issue. 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.<sup>[23]</sup> This issue needs further clarification for transparent and just implementation of compensation policy.

#### Noncompliance of the approved protocol

A clinical trial-related injury or death occurring due to protocol violation or negligence of investigator needs to be compensated as per rule. However, there is no provision under Drugs and Cosmetics Act 1940 to take penal action against the responsible stakeholders even after establishment of relationship in death and negligence. The Medical Council of India (MCI) under MCI Act could cancel the registration of clinical trial as per evidence.<sup>[24]</sup> Penal action is an essential component of any strict enforcement policy and should be considered for issues on trial-related injury or death.

What would happen if protocol is violated by trial participants, for example, occurrence of pregnancy in childbearing age for the trial of category X (teratogenic)

drug? The participant may have been truly informed for using double contraception. In such cases, it is difficult to prove culpability. The guidelines are silent on this issue well.

#### Failure of investigational product to provide intended therapeutic effect

There may be chances of test drug being efficacious/less efficacious due to genetic polymorphism. In this situation, if trial-related injury/death occurs, participant deserves to be compensated. The amendment of rule 122 DAB is expected to cover all issues in this concern. The question arises when clinical trial end point is death, for example, cancer, where participant died because of progression of disease in spite of treatment with standard care. Such cases require individual assessment by experts.

#### Use of placebo in placebo-controlled trial

Guidelines are quite clear that if any injury/death occurs in placebo-controlled trial, participants must be compensated. However, concerns have been raised by many 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.<sup>[25]</sup>

#### Adverse effect due to concomitant medication excluding standard care, necessitated as part of approved protocol

A trial participant can take different concomitant medications along with test drug. These medications may cause adverse effect due to pharmacological property or drug interaction. As per rule participant needs to be compensated if concomitant medication is not the part of standard care for that illness. The concomitant medication is taken as per protocol direction which restricts participant from taking any other medicines of same therapeutic class. Hence, a SAE should be considered to have occurred due to protocol compliance, and participant must be compensated by sponsor.

#### For injury to child in utero because of the participation of parent in clinical trial

Though clearly directed in recent regulation about compensation for clinical trial injury other than death, the assessment of causality is very difficult in this situation and clear set of criteria must be put forth for establishing the same.

#### Inducement for participation

An important consequence of offering blanket compensation for all research-related injury would be the potential for inducement to patients participating in clinical research. It is considered by many that even by providing

free treatment as part of clinical research, there is potential for poor patients to be induced to take part in clinical trials. This problem would get multiplied if in addition to free treatment and management of SAEs, compensation was also provided. Patients would flock to participate in clinical research because not only would they be assured of free treatment, free management of complications arising from even standard treatment in a clinical trial, but also would get monetary compensation for injury or death. This could be a serious problem where the basic principles of clinical research ethics would be compromised.<sup>[26]</sup>

### Pharmaceutical Industry versus Academic/Research Institute

The key players for conducting clinical trials in India are world topmost pharmaceutical companies. The large amount of compensation paid to the participants in case of injury and death would be counted as small fractions of the entire cost of running a sponsored clinical trial and definitely will not affect their budget much. However, the huge amount of compensation as per guideline would possibly affect the investigator-initiated projects in academic and research institutes because these run on shoestring budgets as funding for investigator-initiated research is difficult to obtain. All government scientific organizations are keenly interested to conduct clinical trials to promote the availability of safe and cost-effective treatment to Indian society. The consequences of adopting these guidelines will be a drastic slowdown and eventually a shutdown of investigator-initiated research, which will leave medical research purely in the hands of the industry. Medical costs, already beyond the reach of the common man, will skyrocket manifold and effectively make optimum health care available only to the elite of society.<sup>[26]</sup> In developing countries such as India, it is vital to carry out research to develop cost-effective treatments. There are treatment regimes that are the standard of care in Western countries but are available only to those patients in India who can afford the high costs of treatment.

There is a point of concern that provision of compensation paid in case of participants receiving the standard treatment in life-threatening disease trials, for example, cancer, where the trial end point is death would make research extremely expensive. This will affect individual investigators, academic groups of investigators, and academic institutes to carry out interventional research studies.

Summarily, the robust guidelines for the compensation of clinical trial participants should be able to strike a balance between risk coverage of participants and stimulus for innovation in the field of drug discovery and development.

This will help ensure that medicines with better efficacy and effectiveness are made available at affordable prices to the people.

### CONCLUSION

The Government of India recently amended the rules and regulation in consultation of technical expert for compensation and safety of trial participant which should be appreciated. However, there is a need of clarity on multiple issues which should be discussed with all stakeholders for better understanding of current regulations. In our view, attention must also be given to academic investigators, during discussion to promote availability of cost-effective treatment in India.

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### Conflicts of interest

There are no conflicts of interest.

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