Indian Journal of Dermatology
Indian J Dermatol. 62(4): 387-391

Ethics of Safety Reporting of a Clinical Trial

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DOI: 10.4103/ijd.IJD_273_17
Published in print: Jul-Aug2017

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Clinical trial related injury and serious adverse events (SAE) are a major area of concern. In all such scenarios the investigator is responsible for medical care of the trial participant and also ethically bound to report the event to all the stakeholders of the clinical trial. The trial sponsor is responsible for ongoing safety evaluation of the investigational product, reporting and compensating the participant in case of any SAE. The Ethics Committee and regulatory body of the country are to uphold the ethical principles of beneficence, justice, non-maleficence in such cases. Any

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Abstract

Clinical trial related injury and serious adverse events (SAE) are a major area of concern. In all such scenarios the investigator is responsible for medical care of the trial participant and also ethically bound to report the event to all the stakeholders of the clinical trial. The trial sponsor is responsible for ongoing safety evaluation of the investigational product, reporting and compensating the participant in case of any SAE. The Ethics Committee and regulatory body of the country are to uphold the ethical principles of beneficence, justice, non-maleficence in such cases. Any unwanted and noxious effect of a drug when used in recommended doses is an adverse drug reaction (ADR) whereas if causal association is not yet established it is termed adverse event (AE). An AE or ADR that is associated with death, in-patient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, a congenital anomaly, or is otherwise life threatening is termed as an SAE. The principal investigator reports the event to the licensing authority (DCGI), sponsor and Chairperson of the Ethics Committee (EC) within 24 hours of occurrence of the SAE. This report is furthered by a detailed report by both the investigator and the EC and given to the DCGI who then gives a final decision on the amount of compensation to be given by the sponsor or the sponsor's representative to the grieving party.

What was known?

In routine clinical practice, in case of any adverse events the role of doctor is to ensure that the condition is managed and he/she informs the patients relative and decides the further course of action based on his own judgement or referring the patient to his colleague. The compensation if any is decided by the court of law on the appeal made by the patient/relatives based on misconduct/malpractice.

Introduction

A trial of drugs on human participants must have a record not only of the effectiveness of the drug but also of its safety profile as toxicity outweighs the benefit-risk ratio, making drugs unsuitable for human use. Adverse reactions may be spontaneously reported by a participant to an attending physician, elicited by the investigator during the trial or laboratory related. Such reactions may also be attributed to the drug after the completion of the trial. In all such scenarios, the investigator is responsible for medical care of the trial participant and also ethically bound to report the event to all the stakeholders of the clinical trial. The trial sponsor is responsible for ongoing safety evaluation of an investigational product (IP) and reporting and compensating the participant in case of any serious adverse event (SAE). The Ethics Committee (EC) and regulatory body of the country are to uphold the ethical principles of beneficence, justice, and nonmaleficence in such cases. Thus, to be ethical while conducting trials as investigators or evaluating the safety report as an EC member, it is pertinent to understand the various terminologies used in safety reporting, reporting requirements of adverse reactions, responsibility of the various stakeholders in the trial, causality assessment of an adverse reaction, and guidelines of compensation in case of a SAE.

Terminologies of Safety Reporting

Adverse event

Any untoward medical occurrence (including a symptom/disease or an abnormal laboratory finding) during treatment with a pharmaceutical product in a patient or a human participant not necessarily related to the treatment.[1]

Adverse drug reaction

A noxious and unintended response at doses normally used or tested in humans (in cases of approved pharmaceutical products); a noxious and unintended response at any dose(s) (in cases of new unregistered pharmaceutical products); an untoward medical occurrence seemingly caused by overdosing, abuse/dependence, and interactions with other medicinal products (in clinical trials).[1]

Serious adverse event or serious adverse drug reaction

An adverse event (AE) or adverse drug reaction (ADR) that is associated with death, inpatient hospitalization (in case the study was being conducted on outpatients), prolongation of hospitalization (in case the study was being conducted on inpatients), persistent or significant disability or incapacity, a congenital anomaly or birth defect, or otherwise life-threatening.[1]

Suspected unexpected serious adverse reaction

This term is used to refer to an AE that occurs in a clinical trial subject, which is assessed by the sponsor and/or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study drug. Seriousness criteria have been stated above. Any event which would have led to one of the consequences that fulfill serious criteria but did not, owing to timely medical intervention, may also be deemed a suspected unexpected serious adverse reaction (SUSAR). Such reactions are to be submitted in an expedited manner to the sponsor, Institutional Ethics Committee (IEC), and regulatory authority. Schedule Y does not feature the term "SUSAR" and does not specify expedited reporting requirements for SUSARs; in the event of SUSARs occurring at a foreign site, the procedure and timeframe for reporting to Indian regulators and sites remain undefined.[2]

The clinical trial-related injury and SAE are a major area of concern which has created a climate of mistrust among the study participants and stories of such mishaps are making headlines in the media. Responding to incidents, the Drug Controller General of India (DCGI) has taken stern measures to safeguard the health of clinical trial participants. The Drug and Cosmetics Rule, 6th amendment (DCR-6th Amdmt), with its effective date being June 12, 2015, states the timeliness of reporting AEs in a clinical trial.[3]

Reporting Requirements of Adverse Events/Adverse Drug Reactions

Responsibilities of the investigator

The medical management of the AE/ADR rests on the investigator. According to the DCR-6th Amdmt,[3] the investigator should report all SAEs to the drug regulatory body of India (DCGI), sponsor of the trial, and the concerned EC that approved the trial protocol within 24 h of occurrence of the SAE. If the investigator comes to know about the AE after 24 hours of occurrence, then "occurrence of SAE" is interpreted as "within 24 h of a Principal Investigator (PI) getting to know of the SAE".

The investigator is responsible to further send a detailed report after due analysis to the DCGI, the EC Chairman, and the head of the institution where the trial is being conducted within 14 calendar days of the occurrence of SAE. If the investigator fails to report any SAE within the stipulated period, the reason for the delay to the DCGI along with a copy of the SAE report must be furnished [Figure 1].

View larger version

Figure 1. Timeline for safety reporting in case of serious adverse events

Responsibilities of sponsor

The sponsor must report, after due analysis, any SAE during a clinical trial within 14 days of their occurrence to the DCGI and the EC that approved the study protocol [Figure 1].[3] The sponsor provides the AE reporting forms to the trial site. The sponsor is also responsible for notifying SAEs to the PI, IECs at other trial sites. The study protocol designed by the sponsor must include a financial plan (including insurance) to manage the AEs/ADRs and compensation for trial-related injury.

According to the Indian Good Clinical Practice,[1] Indian Council of Medical Research guidelines,[4] DCRs,[5] the sponsor, whether a pharmaceutical company, or an institution, must agree in a clinical trial agreement before the study begins, to provide medical treatment as well as financial compensation to research participants for any physical or mental injury which they may suffer during the clinical trial. In addition, in the case of study-related death, the participant's legal heir(s) is/are entitled to material compensation. Compensation must also be given to a child injured in utero because of a parent's participation in a trial. The DCR-6th Amdmt states that medical treatment should be provided for as long as required or until such time it is established that the injury is not related to the clinical trial, whichever is earlier. When the participant suffers no permanent injury, the quantum of compensation should be proportionate to the nature of the nonpermanent injury and loss of wages.

Responsibilities of Ethics Committee

The DCR-6th Amdmt states that the EC must provide its report on the SAE, along with its opinion on financial compensation, if any, to be paid by the sponsor or his/her representative, to the DCGI within 30 days of notification by the PI [Figure 1].

Responsibilities of regulatory authority, Drug Controller General of India

In case of SAE, the expert committee constituted by DCGI looks into the inputs from EC and gives it recommendation to DCGI. Depending on the report of expert committee, DCGI determines the compensation of the SAE. If the sponsor fails to provide compensation to a research participant for trial-related injuries or to his/her legal heir in case of death, the DCGI may, after giving an opportunity to show cause why such an order should not be passed, by a written order, suspend or cancel the clinical trial and restrict the sponsor/clinical research organization (CRO)/local representative of a foreign sponsor from conducting any further clinical trials in India or take any other action deemed fit.

Research participants who have suffered physical injury as a result of their participation in a clinical trial are entitled to financial compensation commensurate with their temporary or permanent impairment or disability subject to confirmation from EC. In case of death, their dependents are entitled to material compensation.

Compensation for Serious Adverse Events

The bottom line here is that the financial compensation should be over and above the expenses incurred in the medical management of the trial subject as per DCR 1945.[6] The Ministry of Health and Family Welfare designed formulae to determine the quantum of compensation based on age of the subject, risk assessment depending on the seriousness and severity of the disease, and presence of comorbidity and nature of the injury.

As per the DCR-1st Amdmt[5] and the DCR-6th Amdmt,[3] the sponsor is responsible for compensating the research participant and/or his/her legal heir(s) if the injury or death has occurred due to any of the following reasons:

- Adverse effects of IPs
- Any clinical trial procedures involved in the study
- Violation from approved protocol, scientific misconduct or negligence by the investigator/sponsor/CRO, or other responsible parties
- Failure of an IP to provide intended therapeutic effect where, the standard care, though available, was not provided to the participant as per trial protocol
- Use of a placebo in a placebo-controlled trial where, the standard care, though available, was not provided to the participant as per trial protocol
- Adverse effects due to concomitant medication administered as per the approved protocol
- Injury to a child in utero due to a parent's participation in a clinical trial.

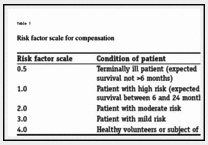
The participant may be paid for the inconvenience and time spent, reimbursed for incurred expenses, and received free medical services in connection with his/her participation as long as required. If the participant suffers from any other brief illness during the ongoing trial, the sponsor also provides ancillary care to participants at the same hospital or trial site.

The compensation would be decided by DCGI after consideration of reports available from EC and the expert committee constituted by DCGI using the following formulas.[78]

Serious adverse event causing death of the subject

The formula for compensation is (B × F × R)/99.37

Where B = Base amount (i.e., 8 lacs); F = Factor determined as per the age (based on Workmen Compensation Act);[7] R = Risk factors [based on seriousness and severity of the disease, presence of comorbidity, and duration of disease of the subject at the time of enrolment, Table 1].



Risk factor scale for compensation

Risk factor scale	Condition of patient
0.5	Terminally ill patient (expected survival not >6 months)
1.0	Patient with high risk (expected survival between 6 and 24 month
2.0	Patient with moderate risk
3.0	Patient with mild risk
4.0	Healthy volunteers or subject of

See full table

Table 1. Risk factor scale for compensation

It was decided that in case of patients whose expected mortality is 90% or more within 30 days, the compensation would be a fixed amount of 2 lacs.

Serious adverse event causing permanent disability

In case of 100% disability, the quantum is fixed at 90% of the amount which would be due for payment in case of death of the subject.[8]

In case of <100% disability, the amount would be proportional to the actual percentage of disability suffered and calculated as below:

(C × D × 90)/(100 × 100), where C = Quantum of compensation in case of death and D = Percentage of disability.

Serious adverse event causing life-threatening disease or reversible serious adverse event in case it is resolved

The quantum is calculated keeping in mind the number of days of hospitalization which results in wage loss of the patient as well as the attendant (thus double wage loss). The wage loss is calculated as per the minimum wage of unskilled worker (in Delhi).[8]

Compensation = 2 × W × N, where W = Minimum wage per day of unskilled worker (in Delhi) and N = number of days of hospitalization.

Serious adverse event causing congenital anomaly or birth defect

Still birth, early death due to anomaly, permanent disability (mental or physical), no death but deformity which can be fully corrected through appropriate intervention are considered under congenital anomaly.[8] If such congenital anomaly arises due to participation of one or both parent in a clinical trial, then

the compensation amount needs to be kept as fixed deposit or alike, so as to bring a monthly interest approximately equivalent half of minimum wage of unskilled worker (in Delhi).[8]

In case of deformities or disabilities, as highlighted above, the medical management needs to be provided by the sponsor over and above the financial compensation.

Timeline for disbursement of compensation

Expert Committee appointed by the DCGI would examine the report of SAE and would give its recommendation to the licensing authority within 30 days. The DCGI must determine the cause of injury or death due to the AE and make the final decision on the amount of compensation to be paid by the sponsor or his/her representative within 150 days of the occurrence of the AE. In case of clinical trial-related injury or death, the sponsor or his/her representative shall pay the compensation as per the order of the DCGI within 30 calendar days of the receipt of such order.[35]

Role of Ethics Committee in determining compensation

ECs of the country are now responsible for recommending the compensation for any trial-related death/injury; thus, it is pertinent that the cause-effect relationship of the trial drug and AE is established.

The EC's opinion to the expert committee or DCGI is only in the form of related or unrelated. Latter applies when it is definitely judged that there is no possibility of the trial intervention/procedure of having contributed to the event.

To know of something that is harmful to another person, who does not know, and not telling, is unethical. Thus, the reporting and disseminating information regarding any AE that might have occurred at any trial site is necessary to keep the pillars of ethics upright under all circumstances of clinical research.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

What is new?

In clinical research, a researcher-doctor must report any adverse event to the ethics committee, institution, the office of DCGI and the sponsor (if any) and manage the adverse event without imposing any financial burden to the research participant.

Acknowledgment

We thankfully acknowledge Prof. Debabrata Bandyopadhyay (Professor and Head, Department of Dermatology, Medical College, Kolkata) and Prof. Avijit Hazra (Professor, Department of Pharmacology, IPGME and R, Kolkata) for reviewing the manuscript and providing valuable inputs.

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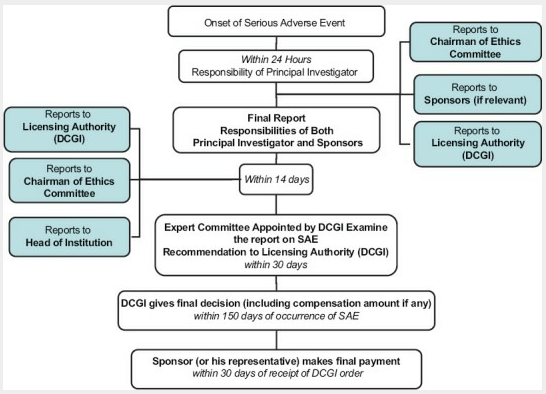

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