Analysis of serious adverse events reports: Review by an Institutional Ethics Committee of a tertiary care teaching hospital

Ganesh Nathuji Dakhale, Mrunalini Vinay Kalikar, Akhil B. Giradkar, Vishakha V. Sinha

Department of Pharmacology, AllIMS, 1Department of Pharmacology, Government Medical College, Nagpur, Maharashtra, India

Abstract

Background: Managing of SAE by all stakeholders i.e. principal investigator (PI), sponsor, and Institutional Ethics Committee (IEC), in an ethical manner is the most important indicator of participant safety during clinical trial. The present study was conducted with the objectives to assess the extent of regulatory compliance in reporting SAEs, relatedness and financial compensation given/recommended by various stakeholders.

Methods: This was a retrospective observational study which involved analysis of SAE's reviewed by IEC. Administrative approval for accessing the documents was obtained and complete confidentiality was maintained. A total of 66 SAE of 34 regulatory clinical trials reported from January 2014 to March 2020 were analyzed.

Result: When analyzed for relatedness, 16 (24.24%) of the reported SAEs were found related to the clinical trial and out of these, 7 were SAE of death. Among the remaining 50 SAE, 48 (72.7%) were not related to clinical trial. 65 (98.48%) SAE reports were submitted to EC within stipulated time as required by regulation.

Conclusion: The study concludes that 66 SAE reports were identified and there was no deviation in reporting timelines in initial reporting and due analysis report by PI and initial review by IEC in 65 SAE's. Similarly, analysis of SAE by IEC for relatedness, and provision of compensation to participant was achieved in majority of SAE. The study is unique in a way that qualitative and quantitative analysis of SAE reports was performed.

Keywords: Compensation, Institutional Ethics Committee, serious adverse events

INTRODUCTION

Participant safety is an important aspect of clinical trials and to enhance it, optimal collection and reporting of serious adverse event (SAE) is important. SAE is defined as any untoward medical occurrence, which results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect (ICH GCP; 1996).[1] SAE has to be reported by the PI and sponsor to the Institutional Ethics Committee (IEC) as well as the regulatory authority (Drugs Controller General of India [DCGI]) within
predefined time lines as per the regulations (New drug and clinical trial rule 2019). With the entire focus of Indian regulations on the safety of human clinical trials participants, SAE reporting has become main responsibility, especially for the sites. As per the Indian regulation, investigator should report all SAEs to the drug regulatory body of India (DCGI), sponsor of the trial, and the concerned Ethics Committee (EC) that approved the trial protocol within 24 h of knowledge of occurrence of the SAE and a detailed report after due analysis to the DCGI, the EC chairman, and the head of the institution within 14 calendar days of the knowledge of occurrence of SAE.

IEC is responsible for recommending the compensation for any trial-related death/injury and to give its considered opinion to the DCGI on both relatedness of the SAE to the clinical trial and the quantum of compensation to be given to the participant within 30 days. Our extensive literature review revealed that there is a paucity of data on the analysis of SAE reports submitted to IECs regarding the relatedness, the actions taken on the SAEs by IECs and DCGI and whether compensation recommended by IEC was approved by DCGI and received by the participant. Considering this fact, it was considered worthwhile to generate the data on the practices followed by principal investigators, IEC and DCGI related to timelines, relatedness, and compensation provided and challenges faced by them.

Hence, the present study was conducted with the following objective:

To assess the extent of regulatory compliance in reporting SAEs, relatedness, and financial compensation given/recommended by various stakeholders.

**MATERIALS AND METHODS**

This study was a retrospective, observational study which involved the analysis of SAE’s reviewed by IEC and was initiated after obtaining approval from IEC of a tertiary care teaching institute in India. The study period was from April 2020 to August 2020. Administrative approval for accessing the documents from the concerned authorities was obtained with strict adherence to the standard operating procedures of the IEC for retrieving the records. Confidentiality agreement was signed with IEC and confidentiality regarding details of the study, participants, investigators, and sponsor was strictly maintained. For every submitted regulatory trial, the documents reviewed by the authors included SAE’s initial report, final detailed analysis report after 14 days by PI, minutes of meeting, any correspondence with PI, compensation recommended by IEC, and granted by DCGI.

A total of 66 SAE of 34 regulatory clinical trials reported from January 2014 to March 2020 were analyzed with following details: (a) Number of initial and follow-up SAE reports, (b) relatedness of SAE to the clinical trial, (c) timelines followed by PI and EC in submitting the SAE as required by regulations, (d) EC’s opinion regarding relatedness and financial compensation to the regulatory authority, (e) compensation recommended by DCGI, (f) sponsor’s response to financial compensation, and (i) Criteria of SAE.

Data were analyzed using the descriptive statistics.

**RESULTS**

A total of 66 SAE of 34 clinical trials received by IEC were analyzed. Of these 34 clinical trials, 19 of them had only a single adverse drug reaction (ADR) reported, whereas 3 of them had 6 ADRs each. The rest 12 clinical trials were found to have ADRs anywhere between 1 and 6. There was representation of phase 2, phase 3, and phase 4 of drug development in the included trials, and none of the trial’s successive phase was carried out at the same site. Furthermore, the ADRs that were seen in the same trial had no obvious similarity [Table 1]. When analyzed for relatedness, 16 (24.24%) of the reported SAEs were found related to the clinical trial and out of these, 7 were SAE of death. Among the remaining 50 SAEs, 48 (72.7%) were not related to clinical trial and in 2 SAE of death, the reason of death could not be ascertained [Table 2].

As far as timelines for reporting are concerned, in 65 (98.48%) SAEs, initial report were submitted to EC within 24 h of occurrence of SAE. The final analysis report was submitted to EC within 14 days of occurrence of SAE in case of 65 (98.48%) of the total SAEs. All the 66 SAE reports were sent by EC within stipulated time of 30 days of the knowledge of occurrence of SAE to CDSCO [Table 3]. In our study, we also observed that free medical management was given by sponsor in almost all cases except one.

We also analyzed the SAE data with regard to compensation. It was revealed that the compensation was recommended by IEC for all the 16 SAE’s related to clinical trial. Out of these, 7 SAE were SAE of death and 9 were SAE other than death related to clinical trial. The compensation was granted by DCGI in 4 out of 7 SAEs of death. Compensation
recommended by IEC and granted by DCGI was same in two cases, whereas in other 2 cases of SAE of death, the amount recommended by IEC was more as compared to the final order passed by DCGI. Among the SAEs other than death also, four were granted compensation. In these, the compensation amount matched in two cases, but in the other two cases, the amount recommended by IEC was less as compared to the final order passed by DCGI [Table 4].

DISCUSSION

Our study was an analysis of SAE reports that the IEC received after the new laws in the year 2013 came into force to assess the extent of compliance of different stakeholders and the way the PI, sponsor, IEC and regulatory authority responded to these reports. Primary finding of the present study is better compliance of the various stake holders in reporting SAE as well as relatedness and granting financial compensation by sponsor to participants/nominees within stipulated period as per regulatory requirement. The year 2013 was a turning point year for clinical research in India with a large number of new regulations introduced to enhance research participant protection, which included SAE reporting time lines and compensation for research related injury to be given by IEC and regulatory body (Drugs and Cosmetics Act; GSR 53E, 2013). In case of SAE of death, the expert committee constituted by DCGI looks into the inputs from IEC and gives recommendation to DCGI. Depending on the report of expert committee, DCGI determines the compensation of the SAE. 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. Therefore, determining the “relatedness” of SAE to the clinical trial is very important.

To the best of our knowledge, this is the first study after amendment in 2013 that analyzed reporting timelines by various stakeholders along with opinion

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Table 1: Categorization of adverse drug reactions according to the phases of clinical trials

| Phase | Number of clinical trials | Number of ADR |
|-------|---------------------------|---------------|
| I     | 23                        | 5             |
| II    | 5                         | 8             |
| III   | 5                         | 5             |
| IV    | 34                        | 66            |

BA/BE = Bioavailability/bioequivalence, ADR = Adverse drug reaction

Table 2: Analysis of serious adverse event relatedness (n=66)

| SAE criteria     | Related, n (%) | Not related, n (%) | Not ascertained, n (%) | Total, n (%) |
|------------------|----------------|--------------------|------------------------|--------------|
| Death            | 7 (11)         | 20 (30)            | 2 (3)                  | 29 (44)      |
| Other than death | 9 (14)         | 28 (42)            | 0                      | 37 (56)      |
| Total            | 16 (24)        | 48 (73)            | 2 (3)                  | 66 (100)     |

SAE = Serious adverse event

Table 3: Analysis of timelines of reporting serious adverse event (n=66)

| Parameter                                      | Yes, n (%) | No, n (%) |
|------------------------------------------------|------------|-----------|
| Was the SAE reported within 24 h to EC by investigator? | 65 (98.48) | 1 (1.5)   |
| Was the final analysis report of the SAE submitted within 14 days to EC by investigator? | 65 (98.48) | 1 (1.5)   |
| Did EC send the analysis report of the SAE to DCGI within 30 days? | 66 (100)   | 0         |

SAE = Serious adverse event, DCGI = Drugs Controller General of India, EC = Ethics committee

Table 4: Analysis of compensation in case of serious adverse event related to clinical trial (n=16)

| Parameter (number of SAE related to clinical trial) | Number of SAE where compensation was recommended by EC, n (%) | Number of SAE where compensation recommended by DCGI, n (%) |
|-----------------------------------------------------|-------------------------------------------------------------|-----------------------------------------------------------|
| SAE of death (7)                                    | 7 (100)                                                     | 4 (57.14)                                                 |
| SAE other than death (9)                            | 9 (100)                                                     | 4 (44.4)                                                  |
| Total SAE (16)                                      | 16 (100)                                                    | 8 (50)                                                    |

SAE = Serious adverse event, DCGI = Drugs Controller General of India, EC = Ethics committee
regarding relatedness of SAE to the clinical trial by PI and EC, compensation recommended by EC along with response from sponsor and regulators for long duration of 6 years. Categorization of SAE was done as death, hospitalization/prolongation of hospitalization and medically significant event [Figure 1].

In the present study, 16 SAE were related to clinical trial, out of which 7 were deaths and the remaining 9 SAE other than death were classified in the category of prolonged hospitalization due to various reasons. Various factors such as preclinical data, temporal association of the adverse event, time-course relationship, comorbid diseases/disorders; concomitant medications, de-challenge, plasma half-life of drug, expected or known adverse events as per the investigator brochure, investigators opinion regarding relatedness, laboratory reports and chronology of events were taken into consideration while deciding the relatedness of SAE. This was verified after evaluation of minutes of meeting of every SAE. Among the nonrelated 48 SAE, there were 20 deaths and the remaining SAE other than death were classified in the category of prolonged hospitalization due to various reasons. Two deaths occurred at home and were notified to EC late as the PI was not aware of it and cause of death as well as relatedness could not be ascertained.

As far as compensation recommended by IEC and granted by DCGI is concerned there was discrepancy in few cases of SAE. The dissimilarity in the compensation amount between IEC and DCGI in 2 cases of SAE of death was due to the difference in the risk factor considered by EC and DCGI. For e.g., in both the cases risk factor considered by DCGI was 0.5 while the same by EC was one. The compensation amount was given by the sponsor to the nominee within stipulated time period and was confirmed by IEC by verifying the cheque received by the nominee.

Unlike the SAEs of death the reason for dissimilarity in compensation amount in SAEs other than death was the difference in the number of days the participant remained under life-threatening situation irrespective of the number of days of hospitalization as considered by IEC and DCGI. As in previous case, sponsor had credited all the financial compensation to participant’s bank account, and this was verified by IEC. Compensation amount as recommended by IEC and granted by sponsor for the “related” SAE ranged from Rs. 4416 to 17.15 lac.

In one study conducted by Tripathi,[7] to review SAE reports by IEC of tertiary care hospital, Mumbai, it was observed that before amendment of Indian regulations of clinical trials as many as 18% nondeath SAEs being labeled as “related,” only one of the 11 SAEs was labeled as related in the AFTER period. Similarly, two of 14 deaths BEFORE and none of the two deaths in the AFTER period were said to be related. Relatedness of SAE is established mainly by hybrid model, i.e., based on opinions of PI and deliberations of persons like IEC and expert committee designated by DCGI. Therefore, there are more chances of variation in decision-making of relatedness of SAE though final decision is taken by expert committee.[8]

For calculation of compensation amount, as a first in the globe, India has introduced robust and well thought out formulae to calculate the quantum of compensation for death and other SAEs (CDSCO, India, 2013).[9] In our study, we found two report where the EC and PI had different opinions of relatedness. Here, according to PI, SAE was unrelated while EC reported it as related to clinical trial. In addition, the IEC often lacks expertise in determining relatedness. Therefore, it is recommended that CDSCO should issue the guidelines for determining relatedness by all stakeholders so as to have standardized procedures.[8]

Both the Indian GCP Guidelines (2001)[10] and the National Ethical Guidelines for Biomedical Research on Human Participants issued by ICMR (2017)[11] have prescribed the need for provision of free medical treatment for an SAE. The amended law (Drugs and Cosmetics Act; GSR 53E, 2013)[9] was more specific in mandating free treatment for all SAEs irrespective of relatedness. In our study, we found that free medical management was given by sponsor in case of all SAE except one that were not related to clinical trial as this was recommended by IEC.

In the case of SAE where free medical management was not given by the sponsor, query was generated by the IEC regarding it after which free medical management was given to the participant. As far as free medical management is considered which is a widely debated issue, it is regarded by many that providing free treatment as part of clinical research, could act as an undue inducement for study participation, especially for poor patients.[12] This problem would get multiplied if in addition to free treatment and management of SAEs, compensation was also provided.[13]

As per the Schedule Y[14] which is now replaced by New drug and clinical trial 2019, all SAEs are to be reported within a specific timeline. In our study, we found that initial report, due analysis report and SAE review by IEC followed standard report timeline except for one SAE where deviation seen in initial reporting and due analysis report. The reason for this was it was captured as
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Conflicts of interest
There are no conflicts of interest.

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The present study is unique in a way that qualitative and quantitative analysis of SAE reports was performed as the content of the SAE report were also analyzed which was not seen in other studies. Therefore, it could also assess the impact of the regulations on the participants directly. However, the present study is limited by the fact that, it is a retrospective audit of SAE received by only one EC, and hence, data generated are not generalizable, but it definitely gives the idea of the regulatory compliance of various stakeholders on following reporting timelines and opinion on relatedness of SAE.

CONCLUSION

The present study evaluated the regulatory compliance of our IEC and focused mainly on SAE reporting by PI and IEC to the regulatory bodies as well as on the issue of compensation in case of related SAE’s. The present study concludes that there was no deviation in reporting timelines in initial reporting and due analysis report by PI and initial review by IEC in majority of SAE’s. Similarly, analysis of SAE by IEC for relatedness, and provision of compensation to participant was achieved in majority of SAE. Hence, it can be said that IEC and PI abide to the law that lead to proper reporting of SAE and accountability of IEC for relatedness and provision of compensation to participant. Finally, to conclude, our study demonstrated clearly that the new regulations have improved regulatory compliance for the reporting and analysis of SAEs by various stakeholders and compensation. It can become more robust if CDSCO gives guidelines to analyze relatedness of SAE.

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AE and later sponsor asked the PI to consider it as SAE. In one study, it was observed that before amendment of Indian regulations of clinical trials reporting was late by 55.6%, whereas SAE reports were delayed by only 18% postamendment.[7] In other study, 25 reports were analyzed, and it was seen that initial report and SAE review by IEC followed standard report timeline, but there was one deviation seen in due analysis report.[15]