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Original Research Article

A retrospective study: root cause analysis of reported serious adverse event and development of corrective action and preventive action for deviated serious adverse event reports at a clinical trial site management office

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ABSTRACT

Background: Serious adverse events (SAEs) are preventable if reported on time. Assessment of harm caused by clinical trials is difficult than assessing the benefits as it relied on the information as recorded by the study team. Hence it is important to have knowledge about quality safety reporting. The objectives of the study were to assess root cause for the timeline deviation found in SAE report and to develop the corrective action and preventive action to minimize deviation rate.
Methods: A retrospective study was conducted in KLE's Hospital and MRC, Belagavi. Data was collected from SAE documented trial study files. Between August 2016 to August 2019, 25 SAE occurred during clinical trials which were included in the study through complete enumeration and purposive sampling.
Results: Data was analyzed for SAE reporting timeline where in no deviation was found in initial report. It was seen that all SAEs were not related to investigational product. The narrations of SAE were according to standardized format as per Ethics Committee review report. A gap was observed between onset of SAE and initial report in 16 case reports.
Conclusions: The study concluded that there was a lag in reporting from onset of SAE to initial report even though there was no deviation observed in the initial report timeline. The main contributing factors were admitting in different hospital without information and lack of knowledge by subjects or their relatives which shows the need of awareness about quality safety reporting.

Keywords: Serious adverse reaction, Investigational product, Ethics committee, Safety reporting, Principal investigator, Corrective action and preventive action

INTRODUCTION

"Clinical trial is a research program conducted on human beings to. Evaluate the medical treatment, investigational medicinal product, or device." The intention of clinical trial is to detect new and improved methods of treatment and prevention, screening and diagnosing different diseases. There are four phases in clinical trial, and each phase is conducted according to applicable regulatory guidelines (ICH-GCP) and approved protocol developed by sponsor.[1]

The Institutional Ethics Committee (IEC) or Institutional Review Board (IRB) and regulatory authority of the country ratify the ethical principles of beneficence, justice, and non-maleficence to protect the safety, dignity

and values of the subjects involved in clinical trial. Thus, while. conducting clinical trial, by all stakeholders to be ethical and must know the terminologies used in safety reporting, requirements for serious adverse event (SAE) /adverse drug reaction (ADR) reporting. Compensation in case of any injury or death occurring during the trial is the responsibility of all stakeholders involved.

Terminologies of safety reporting

Adverse event

Any inappropriate/unexpected medical occurrence (including signs and symptoms, abnormal laboratory findings etc.) during treatment with pharmaceutical investigational medicinal product exposed by subject involved in clinical trial.

ADR

A noxious and unintended response at any doses normally used or tested on specific subjects with investigational product (in cases of approved or new unregistered pharmaceutical products).

SAE

An AE/ADR that is related with hospitalization, life threating events, or death of the subjects involved in clinical trial.

Suspected unexpected serious adverse reaction

During in clinical trial for a certain. investigational product, some subject may experience SAE that may or may not be drug associated but event is unexpected.[2]

During ongoing studies if SAE occurs study team Principal Investigator (PI) is responsible for initial SAE reporting to IEC, Drug Controller General of India (DCGI) and sponsors within 24 hours. Followed by due analysis reporting of SAE to EC, DCGI and sponsor within 14 working days of SAE occurrence. IEC members review the SAE report and provide its opinion on safety concern and financial compensation to the DCGI within 30 days of receiving the report SAE. With a reference of EC opinion and expert committee of DCGI, DCGI determine the quantum of compensation of SAE. Compensation payment by sponsor to subject within 30 days of receipt order from DCGI.[3]

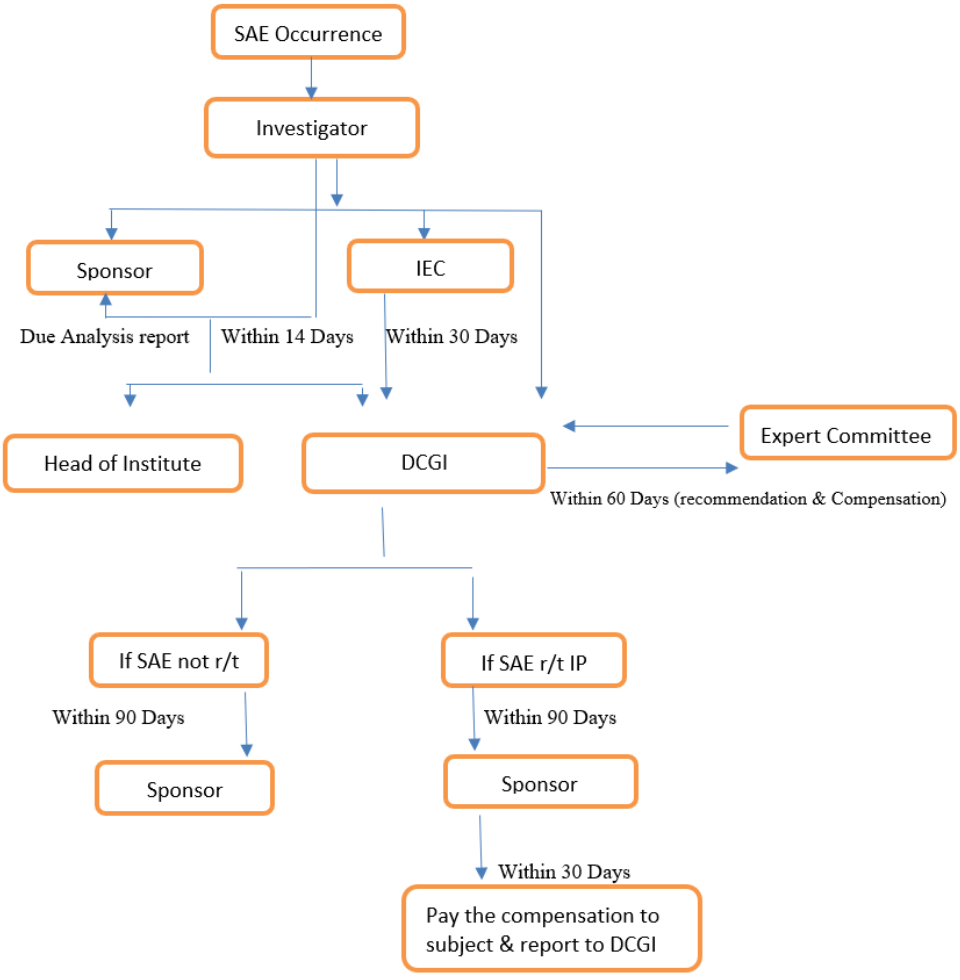

Figure 1: SAE reporting and compensation timeline.

Figure 1 illustrates the SAE reporting timeline & compensation timeline as per the Chapter VI and VII[th] schedule of New Drugs and clinical trial rules-2019.[4]

Safety reporting is a major part of clinical trial related SAE management which can be dealt by root cause analysis (RCA) put forwarded with corrective action. & preventive action (CAPA). RCA is comprehensive term enclosing collections of required problem. solving techniques used to identify the real cause of non-conference or quality problem. In this study RCA is used to know the reason for delay in Safety reporting. The RCA process provides us with a way to identify the cause, that affect the safety reporting with in regulatory SAE reporting guidelines and develop corrective action that contribute to the event and how to prevent future events.[5]

CAPA is a process that inspect and resolves problems, identifies the causes, takes corrective action and prevents repentance of the root cause. Corrective action is an addition part of RCA to find the root cause that. proceed the problem and takes the action directed at the root cause. Preventive action is continued step of corrective action to inhibit the repeatedly occurrence of causes by providing training or developing the principles to cut down the gaps in safety reporting and maintains the quality of safety reporting process.[6]

Clinical trial related AE/ADR/SAE or any injury is a major concern and strictly, periodically safety reporting is the standard. form of action that is taken at site level in order to maintain the quality of safety reporting. At some point there might be a gap in SAE reporting process, hence to reduce the gaps and quality view, we need some basic. principles to observe and minimize the gap in safety reporting process. Here the principles which helps us are, RCA put forward with CAPA which can cut down further safety related issues and maintains the quality of safety reporting. Hence this study was conducted for further understanding related to safety reporting deviations with the objective to assess root cause for the deviation seen in reported SAE as per new drug and clinical trial rule-2019 and to corrective and preventive measures to minimize the deviation rate.

METHODS

A retrospective study was conducted at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi for the period of 6 months (October 2019 To March 2020). The data was collected for the period of 4 months from SAE documented trial study files, through purposive sampling and complete enumeration resulting in 25 study samples. SAE occurred during clinical trials at site level period between August 2016 to August 2019 and descriptive analysis was done. Ethical clearance was obtained from Ethical Committee for human subjects, KLE college of Pharmacy, Belagavi. Confidentiality and non-disclosure agreement were obtained. SAE were reviewed and assessed for occurrence of SAE, actual report to site/study team, initial report timeline, due analysis report by PI, SAE report analysis by IEC members and SAE narrations. Post assessment the SAE files are compared for their respective slandered reporting timelines and evaluated for any deviations. CAPA module was developed once the deviations were seen.

RESULTS

This study was conducted to find deviation in SAE reporting from August 2016 to August 2019. The results showed that, after the assessment of SAE reports, 25 SAE were reported. No deviations were observed in the initial report and SAE review timeline by IEC, but one deviation in due analysis report was seen. Table 1 shows the pattern of SAE reported to site with respective timeline.

Table 1: SAE Report timeline at site.

Parameters	Std. SAE report timeline	Followed standard procedure	Not followed or deviation	Total
Initial report	Within 24 hrs	25	0	25
Due analysis report	14 days of knowledge of occurrence	24	1	25
SAE review by IEC	30 days to initial report	25	0	25

Table 2: Due analysis report.

Due analysis report	Follow up I		Follow up II		Follow up III		Final report	
	f	%	f	%	f	%	f	%
Within 14 days	12	48.0	1	4.0	00	00	12	48.0
Beyond 14 days	1	4.0	8	32.0	4	16.0	12	48.0
Not applicable	12	48.0	16	64.0	21	84.0	1	4.0
Total	25	100.0	25	100.0	25	100.0	25	100.0

On further assessment of due analysis report, it was observed that 48% had their first follow up within 14 days and 4% had their second follow up. But there was no third follow up within 14 days. It was also observed that 4%, 32% and 16% had their first, second and third follow ups beyond 14 days respectively. Final report was seen to be done within 14 days and beyond 14 days by 48% each. The table and graphical presentation of the due analysis report was mentioned in Table 2.

As discussed in Table 1, there was no deviation found in SAE initial reporting. But there was large gap seen in 16 cases between occurrences of SAE to initial report showed in Table 3.

Table 3: Gap in occurrence of SAE to initial report.

Variable	Initial report	
	Frequency	%
On time	9	36.0
Gap b/w onset of SAE to initial report	16	64.0
Total	25	100.0

Table 4: Causative factors for the gap found in SAE reporting.

S. no.	Causative factors	No. of SAE	
		Frequency	%
1	Lack of knowledge by subject relatives	04	25
2	Admitted to other hospital without information	07	44
3	Subject legally acceptance representative negligence to communicate with study team (home death)	02	12
4	Late response by study team	03	19
Total		16	100

While assessing the SAE narration it was found that the main root cause (Table 4) for gap between SAE onset to initial report are as follows. Out of 25 cases, 4 of them had lack of knowledge regarding SAE reporting procedure by subject/legally acceptance representative (LAR). Due to requirement of emergency treatment, 7 got admitted to their nearest hospitals, which led to delay in reporting to PI. Negligence in reporting of SAE by LAR were seen in 2 cases due to death of subject at home. Interruption in reporting were seen in 3 cases because of late response by study team.

25 SAE reports found at site from August 2016 to August 2019 were not related to investigational medicinal product (IP) (Table 5). As per the EC review report all SAE narration followed standard procedure (Table 6). Out of 25 SAE, 72% were recovered, 20% succumbed to death and 8% had withdrawn from the study (Table 7).

Table 5: SAE related to IP.

SAE	Related to IP	Not related to IP	Total
	0	25	25

Table 6: SAE narration.

SAE narration	Followed std. procedure	Not followed	Total
	25	0	25

Table 7: Outcomes of SAE.

SAE	Out come	
	Frequency	Percentage
Recovered	18	72.0
Death	5	20.0
Withdrawn from study	2	8.0
Total	25	100.0

CAPA module

This study suggests that implementation of following CAPA to provide effective information and minimize the gaps occurred in SAE occurrence to initial report which will also improve the quality of the safety reporting process (Table 8).

Table 8: CAPA module.

Causative factors	CAPA
Lack of knowledge by subject relatives (n=4) (25%)	Periodical telephonic training to participant/LAR.
	Pre-recording the procedure which can be reminded on participant's requirements.
	Develop and Implement IEC technique to standardize the communication method
	Making and providing of flow charts, pamphlets which includes safety reporting procedure in local language.

Continued.

Causative factors	CAPA
Admitted to other hospital without information (n=7) (44%)	Develop e-device of automated SAE detection that is attached to patient.
	GPS tracking device to track the patient.
	Develop an universal mark on participant hand that identifies as clinical trial participant understand only by medical professional.
Subject LAR negligence to communicate with study team (n=2) (12%)	Educate and encourage the report of all events related to drug during clinical trial.
	Create awareness regarding the importance of safety reporting
	Psychological support to patient and patient relatives.
Late response by study team (n=03) (19%)	Develop a patient oriented quick repose team
	Collaboration of multidisciplinary team
	Up gradation of knowledge &skills of study team

n=sample size.

DISCUSSION

A retrospective study was conducted in KLES Dr. Prabhakar Kore Hospital and MRC Belagavi. Data were collected from SAE clinical trial files. 25 reports of SAE were included through complete enumeration and purposive sampling.

SAE were assessed for root cause analysis including occurrence of SAE, actual report to site and personnel, initial report timeline, due analysis report by the PI, SAE report analysis by the IEC members and SAE narrations and further CAPA was developed to help in minimizing deviation rate.

In this 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. Similarly, a study conducted in USA by Hughes to identify the differences in reporting SAE in industry sponsored clinical trials registries and journal articles on antidepressant and antipsychotic drugs was done which showed that out of 1608 SAEs, 60% had no description. Most cases of deaths and suicides were not reported in articles. The trials with zero SAEs were 2.35 times more likely to be published giving out incomplete information to clinicians.[8]

Another study conducted by Tripahi in Mumbai, to review SAE reports by IEC of tertiary care hospital, Mumbai 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% post amendment. Seventeen median days were taken in SAE reporting before and 5 median days after amendment respectively stating the poor compliance in reporting before amendment.[14]

In current study, as per the EC review report all SAE narration followed standard procedure and was not related to investigational product. Also, a study conducted in US by Moore, evaluated the reports received by FDA where in out of 528,192 fatal outcomes, 4.7% were directly by health professionals and consumers and 95.3% by drug manufacturers. Report completeness from drug manufactures was seen to be poor lacking the event date, gender, age compared to direct submission by agency.[16]

In the present study outcomes of patients have been reported where in 72% were recovered, 20 were dead and 8% had withdrawn from the study. Quality assessment of SAE reporting to academic sponsors of clinical trials was done in France over 247 reports where in seriousness of the event was unknown in 3.6% of the reports and causality assessment was missing in 9.3%. There was lack of information in 15% of the reports with missing onset date of SAE in 5.7% and patient outcome in 12.1%. Completeness and accuracy of the reporting was seen to be far from the optimal level which was in contrast to this study.[7]

A gap between the onset of SAE and initial reporting was identified in 16 cases out of 25 reports in this study after the in-depth analysis. The causative factors were mainly being admitted to different hospital without information, lack of knowledge by subjects/participant or relatives, late response by study team and LAR negligence to communicate with study team with 44%, 25%, 19% and 12% respectively. Similar study conducted in US for root cause analysis of SAE among older patients identified lack of communication with 43.9% being the most common underlying cause for SAEs occurrence.[12]

A CAPA model was also formed in this study including training of the study team and the participant/subjects, effective communication skills, use of GPS tracking system and Information Education Communication (IEC) activities for awareness with advice on implementation. A similar study in China developed a computer assisted Adverse Drug event alarm and assessment system for hospital in patients with automated screening, assisted evaluation, risk analysis and spontaneous reporting system.[11]

CONCLUSION

This study focused on quality of SAE reporting by principal investigator to the regulatory bodies. On time reporting of safety report is an essential part of

participant safety. By doing a retrospective assessment, concludes that 25 SAE reports were identified & there was no deviation in initial reporting but there was a deviation seen in due analysis report when compared with standardized SAEs reporting timeline guidelines. It was observed that all SAEs were not related to investigational product and also, the narrations of SAEs followed the standardized procedure when reviewed by Ethical Committee. On further analysis, it was seen that there was a large gap in initial reporting after the onset of SAEs which helped in the development of CAPA module which is stressing on communication and awareness about importance of safety reporting.

Recommendations

Research can be conducted on the larger sample. Assessment of compensation amount paid by sponsors within timeline can be done. Effective implementation of CAPA model with further improvement in quality of SAE reporting.

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