***Abstract:***

*The off-site SAE reports received by Institutional Ethics Committee (IEC) for review of causality assessment as part of CIOMS Periodic Drug-Safety Update . The principal investigators (PIs) and sponsors state their causality. The present study was designed to assess these CIOMs report and evaluate the degree of agreement among them. Reports submitted to the IEC between October 2013 and December 2014 were reviewed. The offsite SAE reports were evaluated for different study criteria such as number of received / project, number of initial and FU reports / project, number of specific offsite SAE based on SAE term classification, assessment of causality by PI and sponsor, IEC Review process of the offsite SAE reports in terms of number of meetings and number of reports reviewed per meeting and action taken by IEC. A total of 1583 reports were analyzed. The median number of reports per project is 42. Maximum SAE offsite reports were received from drug trials of endocrine diseases and least number with cardiac diseases trials. In initial reports causality agreement matched for relatedness only in 46 (7%) reports between the PI and the Sponsor and for not relatedness matched only in 303 (48%)reports. While in initial reports with follow up causality matched for relatedness in 35 of 174(20%) in initial and 65 of 260 (25%) in Follow-up. For not related it matched in 72 of 200 (36%) in initial and 108 of 292(37% )in FU reports.*

*Mean duration of SAE subcommittee meetings was 31.87 ± 6.95 minutes and mean number of agenda items was 1.8 ± 0.65. The offsite SAE reports form a major document burden for EC and does not receive the vigilant scrutiny as the onsite SAE report.*

**INTRODUCTION**

The primary responsibility of an Institutional Ethics Committee (IEC)/ Institutional Review Board (IRB) is to ensure safety of research participants and safeguard their welfare and rights. To fulfill this responsibility, the IEC performs initial review and approval of a clinical study and conducts continuing review of the study at intervals appropriate to the degree of risk presented in the study. As a part of the continuing review process, the IEC also evaluates serious adverse events (SAE) that occur at the site as well as those from other sites involved in the same study (1).

Suspected Unexpected Serious Adverse event Reports (SUSAR) are reports of adverse events that at any dose result in death; are life threatening; require hospitalization or prolongation of existing hospitalization; result in persistent or significant disability or incapacity; or lead to congenital anomaly or birth defect (2).These events are reported by the investigators to the sponsors within a specific timeline. As per ICH-GCP, it is the responsibility of the sponsor to inform all the other investigators involved in the same study about the Off-site SAEs which have occurred at any one of the sites. Further, the PI then informs the IEC of these Off-site SAEs (3).

However, there are no guidelines at present which recommend the process for ethical review of these offsite SAEs (4). Against this background, this study was conceived to analyze the Off-site SAE reports received by the IEC in the year of 2013-14 in terms of type of reports, number of reports per therapeutic area and SAE term classification with the objective to review the causality assessment stated by the principal investigators (PIs) and sponsors and evaluate the degree of agreement among them. In addition, the review process for offsite SAE and action taken by the IEC towards the Off-site SAE reports was also evaluated.

**METHODOLOGY**

The study was initiated following approval of the Institutional Ethics Committee of Seth GS Medical College, Parel, Mumbai (EC/OA-123/2014).This was a retrospective study wherein the Off-site SAE reports submitted to the IEC between October 2013 and December 2014 were reviewed. The Off-site SAE reports which fulfilled the following selection criteria were included.

Inclusion criteria: Off site SAE report was:

a) From Pharmaceutical Industry sponsored studies

b) Completely filled report

c) Having causality of the SAE reported in terms of related or non related

Off site SAE reports were excluded if the reports had any item which was kept blank or if the causality was stated in terms other than related or non related (e.g. suspected /unsuspected or expected / unexpected)

The Off-site SAE reports were evaluated for the following items:

* Number of Off-site received / project
* Number of initial and FU reports / project
* Number of initial reports having a follow up report and number of only initial reports
* Number of specific offsite SAE based on SAE term classification
* Difference in timelines between the onset date and reporting date
* Assessment of causality by PI
* Assessment of causality by sponsor
* Change in causality in the two datasets a. Only initial offsite reports b. Initial offsite report with follow up reports
* IEC Review process of the Off-site SAE reports in terms of number of meetings (full board and SAE subcommittee) and number of reports reviewed per meeting.
* Action taken by IEC towards the offsite SAE report

The names of the trials, sponsor and the investigator were not disclosed as well as confidentiality of all the documents reviewed was strictly maintained.

**STATISTICAL ANALYSIS**

Descriptive statistical analysis was conducted for each item using Microsoft Excel 2013.

**RESULTS**

During the study period Oct. 2013- Dec. 2014 (15 months) the total number of pharmaceutical industry sponsored studies approved by the IEC / ongoing was 30. Out of these, two studies were terminated by the sponsor after IEC approval at the site as global recruitment was over. Sponsors forwarded offsite SAE reports for the remaining 19 clinical trials out of the total 28 studies. The Phase wise distribution of these19 clinical trials was as follows: Phase II- 4, Phase III- 13 and =1Phase IV- 2 trials. Out of the 19 clinical trials, 13were double blind, randomized, controlled (5 of which were placebo controlled) trials and the remaining 6 were open labeled studies. The investigational new drug was a new chemical entity in 15 clinical trials, while in 2 trials the investigational product was a biologic agent while 2 trials involved stem cells as intervention. The trials involved the following therapeutic areas: neurological diseases: 5 (Epilepsy – n=3, Resistant depression – n=1 and Multiple Sclerosis – n=1); cardiac diseases:2 (Heart failure - n=1 and 1 on acute coronary syndrome), endocrine diseases: 3 (Diabetes – n=2 and Postmenopausal osteoporosis -n=1), Autoimmune diseases: 6, and Infective diseases:3.

These 19 studies reported a total of 1704 Off-site SAE reports to the IEC office during this period. A total of 121 Off-site SAE reports were excluded from the analysis as they did not fulfill inclusion criteria. Thus, 1583 Off-site SAE reports were analyzed. Of these 1583 reports, 627 were only initial reports , 246 initial with follow up ( 368) reports and remaining 342 were only follow-up reports. The median number of Off-site SAE reports per project was 42 (Interquartile range as 2-118). The median of initial reports /per project was 26 (Interquartile range 2- 76) and of follow up reports / project was 16 (Interquartile range 1- 42). The number of SAE reports received for given therapeutic area is presented in **Table 1**.The maximum number of SAE offsite reports were received from projects involving drug trials of endocrine diseases and least number with drug trials involving cardiac diseases (refer **Table 1**). The number of offsite SAE reports per project and per country of origin of the report is depicted in **Table 2**. The United States of America had reported the highest number of offsite SAE per project. During the same period the number of onsite SAE reports was 43 (19 initial SAE reports and 24 follow up reports) which were received from 9 projects only in our IEC.

The total number of SAE terms stated in the 1583 reports was 2103 which were further classified according to the Common Terminology Criteria for Adverse Events (CTCAEv3.0) and are presented in **Table 3**. The maximum number of offsite SAEs were from the Metabolic/ laboratory section (285) followed by vascular section (205). The 1583 SAEs came from 1291patients (1.22/patient) with 789 males and 502 females. The mean age was 54.32 + 17.96 years. Out of the 1291 patients,40/1291 (3.1 %) were children (Aged[mean ± SD]: 9 .08 ± 5.85) coming from3 projects being conducted in the therapeutic area of epilepsy. Similarly 580 (45%)(Aged [mean ± SD]: 71.38 ± 4.76 ) were geriatric patients (age >65 years ). These were enrolled in: 3 projects in epilepsy, 2 projects in DM, 2 projects in chronic hepatitis B infection and 1 project on postmenopausal osteoporosis.

In the data set of only initial reports, according to the PI, the SAE was related to the clinical trial in 321/627(51.2%) and 303/627 (48.3%) were not related while 3 were not available. According to the sponsor however only 46/627 (7.3%) reports were related to the clinical trial while 513/627 (81.8% ) were not related and 68 reports were not available. For related reports the causality between the PI and the sponsor matched only in 46 (7.3%) reports and for not-related reports in 303(48.3%).

In the data set of initial reports ( n=246) with follow-up reports, the PI stated related as causality in 174/246 (70.7%) and not related in 72/246 (29.3%). This was associated with 368 follow-up reports in which PI stated causality as related in 260/368 (70% ) and not related in 108/368 (29.3% ).The PI changed causality from related to not related in 17 cases not related to related in 6 cases. The sponsor stated causality as related in 35/246 (14.2%) and not related in 200/246(81.3%) and it was not available in 11 cases. In follow-up reports the sponsor stated causality as related in 65/368(17.7%) not related in 292/368(79.3%) reports while 11 reports were not available. The sponsor changed causality from related to not related in 9 cases while none in not related to related. In initial reports for related cases the causality matched only in 35/246 (14.2%) reports while for not related cases it matched in 72/246(29.3%) reports. While in followup reports causality match for related reports was 65/368(17%) and for not related it was108/368(29%).

The median time duration between onset of SAE and date of reporting the off site reports to our IEC was 143 days (Inter quartile range 12 – 557 days). The IEC had reviewed these offsite SAE reports in 40 SAE subcommittee meetings and 14 full board meetings. The mean duration of the SAE subcommittee meetings was 31.87 ± 6.95 minutes and mean number of agenda items was 1.8 ± 0.65. The median number of Off-site SAE reports reviewed per meeting were 12 (Interquartile range 2- 26). The IEC had reviewed the offsite SAE reports and sent notification letters to the PI.

**DISCUSSION**

Our study found that 19 clinical trials (of which 13were double blind, RCTs and 6 open labeled) reported a total of 1704 Off-site SAE reports to the IEC office during our study period of which 1583 fulfilled eligibility criteria for analysis. The total number of initial reports was 627 and initial with follow up reports was 246 (initial reports /per project 26 (Interquartile range 2- 76) and follow up reports / project was 16 (Interquartile range 1- 42). As this was a fixed duration study the number of initial reports was higher than the initial with follow up reports. Some of the follow up reports must have arrived to the IEC office after the referral period of the study. ( This can be viewed as the limitation of this study).

The maximum number of reports were received from projects involving drug trials of endocrine diseases and least number from drug trials involving cardiac diseases. During the same period the number of onsite SAE reports was 43 (19 initial SAE reports and 24 follow up reports) which were received from 9 projects only.

To safeguard patient well-fare and maintain his/her dignity is a mandatory and primary responsibility of the EC. In this context reviewing on site SAE reports, and ensuring free treatment and compensation to the trial participant forms the primary function of the EC. Reviewing offsite SAE reports is an additional task for the EC to ensure patient safety. From our study it is evident that review of offsite SAE reports involved a huge magnitude of work as reflected from the 1704 offsite reports versus 43 onsite SAE reports received during the study tenure. It is expected that the EC in its review of these offsite SAE reports may suggest additional safeguards which may warrant change in the IB, protocol or ICD. Reviewing this secondary data by the EC is a Herculean task. As seen in our study, our EC received 105 reports per month which were reviewed in 2.6 / month SAE sub-committee meetings and approximately 1 full-board meeting per month. In view of this data being from all over the globe, with very little data available for analysis (as well as the fact that this may be blinded data) it is a very challenging task to review the data and reach meaningful conclusions. There is no available literature in review of Off-site reports. More importantly, no guideline (including the ICMR- Ethical Guidelines for Biomedical Research) mentions how to review the Off-site SAEs.

In addition, there were a wide variety of investigational agents being evaluated in clinical trials extending over a variety of therapeutic areas ranging from neurology, cardiology and endocrinology. During project review these projects in addition to review by EC members were also sent to subject experts for review. However, all offsite SAE reports were reviewed and noted by the SAE Subcommittee or the IEC. It is important to note that even Schedule Y does not make it mandatory (it is only written as “preferable”) to have a medical pharmacologist on an EC that reviews clinical trials. Currently the schedule Y has been replaced by new notification GSR 227 E, however the clause remains the same .(5) Do all ECs have the competence to review Off-site SAE reports, assess the causality and opine if additional safeguards are needed. It can be argued that this is the job clearly spelt out for the Data Safety Monitoring Committee, which has access to more safety information and all of the data at the time of review unlike an EC which would receive this information piecemeal.

As per GSR 287 dated 8th March 2016 (6), the Licensing Authority of India for drug trials involving new drug has stated that the sponsor shall have a Pharmacovigilance system in place and this system shall be managed by qualified and trained personnel who are responsible for collection and analysis of adverse drug reaction reports. In this context do EC members receive any training regarding due analysis of SAE reports and have the expertise for review?

The other finding in our study that merits attention is the mismatch between PI and sponsor on the causality assessment. The causality assessment was stated as related by the PI in as many as 70 % cases while sponsor stated related in only 14. 2% of the total reports. This mismatch can happen as PI is dealing with the patient and he is actually aware of the presenting event and also with past history of the disease. He is in a better position to opine on causality for that particular case as he is dealing with primary data. The sponsor is also like the EC dealing with secondary data. But at the sponsor’s end the primary SAE report is scrutinized by the pharmacovigilance team of the sponsor. This team does have data pertaining to the case and also cumulative and collateral data of similar cases that experienced the event with the same drug in different trials. Thus, the pharmacovigilance team from the sponsor side does make causality opinion based on the case data in the background of huge collateral data which may drive the opinion to be non-related. However, that the sponsor has voted as “unrelated” what the PI has written as related in as many as half the SAEs received indicates a major area that needs to be addressed. More justification on part of the sponsor is needed if this kind of “downgrading” of causality is to be done as in India the issue extends to the need for payment of compensation in case of a related SAE.

The EC is also reviewing secondary data but unlike the pharmacovigilance team does not have access to the background data and may also have time constraints in deriving this opinion. The EC has to approve projects/ amendments and review onsite SAE reports and these take up the major time / discussion in the meetings. The offsite SAE reports may not receive the same depth of scrutiny from the EC as the onsite report for terms of causality opinion. This is evident in our study as the EC has only noted all the offsite SAE reports.

The median time between onset of SAE and date of reporting the Off-site SAE to our IEC was 143 days with an Inter quartile range 12 – 557 days. Even if the EC were to raise any concern regarding the change in risk benefit assessment after reviewing this report it is too late to make any difference. Additionally, if the EC needed more information it would require far too long for this information to reach back to the EC to be meaningful. Further, if the EC does, based on offsite SAE reports request the sponsor to amend the protocol or ICD it is difficult for the sponsor to correct them when the parent IEC which had reviewed the onsite SAE did not seek any clarifications.

In addition, there are no reporting timelines required for offsite SAE to be submitted to PI or EC by the sponsor. All regulations (ICH-GCP; ICMR guidelines and Schedule Y and its amendments) (7,8) mandate reporting within a time period for onsite SAE but no timelines are described for offsite SAE (for e.g. sponsor will submit onsite SAE report to given IEC in 14 days but other sites/ ECs do not receive this report in 14 days). In addition, all national and international ethical guidelines have listed reviewing offsite SAE as one of the functions of the EC. If no remedial measures can be sought is it worth putting time and effort in reviewing these offsite SAE reported to the EC?

In our study more SAEs were reported pertaining to metabolic / laboratory investigations abnormalities followed by vascular events. As stated earlier, all trials did have safety monitoring as one of their objectives and investigations such as LFT, RFT, blood counts were routinely done at repeated intervals in these projects. The vascular section SAE were also on rise as they reflected ACS (Acute Coronary Syndrome) and CVA (Cerebrovascular Accident) which were reported more from the projects catering to endocrine diseases. As these projects were long term studies hence safety follow up was also extensive. Most offsite SAE reports were received from projects involving endocrine diseases as these projects were long term studies, had more sample size and were multinational, multi-centric studies. In addition, these studies recruited elderly population which is more prone to develop SAE due to disease progression, concomitant medications and drug interactions. The offsite SAE reports were less in number for projects involving cardiac diseases. The reasons for this could be because they were short term trials and the protocol stated that cardiac events were the end points and not counted as SAE. Similarly as a country, India contributed to only 96 reports out of the total 1583 reports whether it was worth reviewing the other 1500 offsite reports received from various countries is also an issue.

The other point of concern is that the SAE reporting form varies in different countries. Though most of the pharmaceutical companies while reporting offsite SAE utilize the Off-site SAE form given by CIOMS and forward the same form to all sites globally, there can be variation in reporting causality. Sponsors may use the term suspected and not suspected or expected and unexpected or resort to WHO UMC scale as probably/ possibly related or unrelated while reporting causality. In India the term relatedness can mean related to drug or trial procedure whereas internationally it is only in context with the drug (9).

Importantly, of the 1704 reports as many as 121 reports had missing information. It is well documented that regulators of a given country review all the SAE reports which have occurred in their patient population. Regulators, and ECs can demand change in protocol, IB, ICD or even demand suspension of the trial. In view of this, why should an IEC review these Off-site SAE reports and spend precious time and resources doing so.

The limitations of our study is that it is record / document analysis study and we did not interview investigators regarding their opinion on causality or the change in the risk benefit assessment due to the occurrence of offsite SAEs.

**CONCLUSION**

The offsite SAE reports do form a major document burden for the EC and does not receive the vigilant scrutiny as the onsite SAE report. Ethical guidelines do mention that these reports must be reviewed but do not state any action plan for the EC. Long term studies do generate large number of offsite SAE reports and most common SAEs featuring in laboratory investigation abnormalities section. We recommend that Off-site SAE reports not be submitted to IECs – rather DSMB reports may be given to IECs along with any recommendations made. This would save time for the IEC to focus on local site safety issues and continuing oversight of a project.

**ACKNOWLEGEMENT**

We acknowledge Dr. Anirudha Potey for providing statistical helping and we also acknowledge Mrs. Janhavi Katakar for her supervision for the entire SAE reporting.

**TABLE 1: Number of offsite SAE reports received**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Therapeutic area** | **No. of projects** | **No. of offsite SAE reports received in 15 months** | **No. of offsite SAE /projects in a given therapeutic area** | **Average duration of trials (years)** |
| Neurological diseases | 5 | 347 | 69.4 | 5.1 |
| Cardiac diseases | 2 | 10 | 5 | 3.2 |
| Endocrine diseases | 3 | 974 | 324.6 | 3.5 |
| Autoimmune diseases | 6 | 74 | 12.3 | 3.9 |
| Infective diseases | 3 | 178 | 59.3 | 2.3 |
| **Total** | 19 | 1583 |  |  |

**Table 2: Country-wise distribution of offsite SAE reports**

|  |  |  |  |
| --- | --- | --- | --- |
| **Country** | **Total number of offsite SAE reports** | **Total number projects for which offsite SAE reports received** | **Off site SAE Reports/project/country** |
| Australia | 45 | 5 | 9 |
| Belgium | 21 | 5 | 4.2 |
| Brazil | 87 | 9 | 9.67 |
| Bulgaria | 8 | 2 | 4.00 |
| Canada | 41 | 8 | 5.13 |
| Chile | 2 | 1 | 2.00 |
| Czech | 16 | 4 | 4.00 |
| Denmark | 7 | 1 | 7.00 |
| Finland | 64 | 2 | 32.00 |
| France | 34 | 8 | 4.25 |
| Germany | 74 | 9 | 8.22 |
| Greece | 11 | 3 | 3.67 |
| Hongkong | 25 | 5 | 5.00 |
| Hungary | 4 | 3 | 1.33 |
| India | 96 | 10 | 9.60 |
| Ireland | 1 | 1 | 1.00 |
| Israel | 31 | 3 | 10.33 |
| Italy | 29 | 6 | 4.83 |
| Japan | 2 | 1 | 2.00 |
| Korea | 28 | 3 | 9.33 |
| Mexico | 15 | 7 | 2.14 |
| Netherlands | 31 | 9 | 3.44 |
| Norway | 9 | 4 | 2.25 |
| NZ | 6 | 4 | 1.50 |
| Poland | 141 | 9 | 15.67 |
| Portugal | 2 | 1 | 2.00 |
| Romania | 25 | 5 | 5.00 |
| Russia | 46 | 8 | 5.75 |
| SA | 12 | 2 | 6.00 |
| Serbia | 19 | 2 | 9.50 |
| Singapore | 6 | 2 | 3.00 |
| Spain | 40 | 8 | 5.00 |
| Sweden | 8 | 1 | 8.00 |
| Switzerland | 5 | 2 | 2.50 |
| Taiwan | 12 | 6 | 2.00 |
| Tunisia | 4 | 3 | 1.33 |
| Turkey | 49 | 3 | 16.33 |
| UK | 84 | 9 | 9.33 |
| Ukraine | 7 | 2 | 3.50 |
| US | 436 | 9 | 48.44 |
| **Total** | 1583 |  |  |

**Table 3: Distribution of SAE terms**

|  |  |
| --- | --- |
| **System** | **Number of SAE terms** |
| Allergy/ Immunology | 106 |
| Auditory | 8 |
| Blood / Bone marrow | 36 |
| Cardiac arrhythmia | 89 |
| Cardiac general | 66 |
| Coagulation | 33 |
| Constitutional symptoms | 58 |
| Death | 8 |
| Dermatology | 63 |
| Endocrine | 56 |
| Gastrointestinal | 189 |
| Growth and development | 1 |
| Haemorrhage / Bleeding | 42 |
| Hepatobiliary / Pancreas | 152 |
| Infection | 63 |
| Lymphatics | 16 |
| Metabolic /Laboratory | 285 |
| Musculoskeletal / soft tissue | 176 |
| Neurology | 109 |
| Ocular | 14 |
| Pain | 71 |
| Pulmonary / Respiratory | 69 |
| Renal / Genitourinary | 73 |
| Secondary malignancy | 95 |
| Sexual reproductive function | 17 |
| Surgery/ intra-operative injury | 34 |
| Syndrome | 19 |
| Vascular | 205 |
| Total | 2153 |

**RFERENCES**

1. "Law Relatings To Drugs & Cosmetics". *Cdsco.Nic.In*, 2017. Available from [http://www.cdsco.nic.in/html/GCP1.html. Last](http://www.cdsco.nic.in/html/GCP1.html.%20Last) accessed on 04/05/2019.

2. What is a Serious Adverse Event? Available from

<https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event>. Last accessed on 04.05.2019.

3. Clinical safety data management: definitions and standards for expedited reporting e2a .*Ich.Org*, 1994. Available from <https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf> .

4. Brahmachari, Ballari, Melanie Fernandes, and Arun Bhatt. "Pharmacovigilance For Clinical Trials In India: Current Practice And Areas For Reform". *Perspectives In Clinical Research*2, no. 2 (2011): 49. doi:10.4103/2229-3485.80366.

5. GSR 227 (E). Available from

6. GSR 287 (E). Available from <https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=MTA2Mg==> . Last accessed on 04.05.2019.

7. *ICMR guidelines.* Available from <https://icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf> Last accessed on 04.05.2019.

8.  *Schedule Y. Available from* [http://cdsco.nic.in/html/D HYPERLINK "http://cdsco.nic.in/html/D&C\_Rules\_Schedule\_Y.pdf"& HYPERLINK "http://cdsco.nic.in/html/D&C\_Rules\_Schedule\_Y.pdf"C\_Rules\_Schedule\_Y.pdf](http://cdsco.nic.in/html/D%26C_Rules_Schedule_Y.pdf). Last accessed on 04.05.2019.

9. The use of the WHO-UMC system for standardised case causality assessment. Available from [https://www.who.int/medicines/areas/quality\_safety/safety\_efficacy/WHOcausality\_assessment.pdf. Last](https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf.%20Last) accessed on 04.05.2019.