**SLUG: ARTICLE**

**TITLE: A Retrospective Analysis of Reports of Site Monitoring Visits by The Institutional Ethics Committees in An Indian Tertiary Care Hospital**

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***Abstract***:

*Monitoring of clinical trials is an integral part of functions by the institutional ethics committee, to ensure ethical conduct of research. According to the 2017 ICMR Guidelines for Research, there is a strong need for active monitoring of clinical trials. A previous study done by the authors had found many lapses after site monitoring, for researches initiated between 2008 and 2010. In this research 12 clinical studies, both sponsored and investigator initiated, were monitored by the members of the IEC, in the past seven years (2011-2017). The most common violation was seen related to informed consent issues, at 8 out of 12 sites. The other violation themes were lack of investigator’s understanding of protocol (6/12), deviation from investigational plan (5/12), non-reporting of study progress to IEC (4/12), patient recruitment prior to IEC approval (2/12). The IEC took various corrective actions like ordering for re-consent, GCP re-training, asking explanations for deviations, asking interim reports, facility upgradation and paying of pending compensation. IEC stopped reviewing protocols from that PI site and study recruitment was kept on hold for the same PI for multiple lapses. Our study perhaps ascertains that active site monitoring by Ethics Committee is a must to ensure ethical conduct of studies.*

Keywords: IEC, Study Monitoring, Ethics Committee, India

1. Previous submission of similar work: A study to find the EC monitoring practices at KEM Hospital from 2008-2010 was published in IJME (Reference: *Shetty YC, Marathe P, Kamat S, ThatteU.Continuing Oversight Through Site Monitoring: Experiences of An Institutional Ethics Committee In An Indian Tertiary-Care Hospital. IJME. 2012;9(1):22-26.*) This study was planned as a follow-up to the previous study conducted, toanalyze the reports of site monitoring visits made by the IECs in the past seven years (2011-2017) and compare the practices now with the past findings from (2008-2010).

**Introduction**

Monitoring is the act of overseeing the progress of a clinical trial, which helps in ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirements (1). Declaration of Helsinki mentions that the ethics committee must have the right to monitor ongoing studies so that they can be conducted in the best way possible (2). In United States of America (USA),the ethics committees are entrusted with the initial review of the proposed interventional research protocols prior to project initiation and continuing responsibility of regular monitoring for the necessary Ethics compliance till completed (3).

In India, it is positive to see that the clinical trial monitoring scenario is changing. The DCGI office has monitored institutional ethics committees (IECs)by site inspection and by reviewing the re- registration form of ethics committee with the Central Drugs Standard Control Organisation (CDSCO) which has monitoring as a pre requisite and investigator site (oversight??) to ensure ethical conduct of clinical studies. Numerous updates to policy and guidelines governing clinical research in India have been introduced by the Indian regulatory authority which includes the National Accreditation Board for Hospitals and Healthcare Providers (NABH), Quality Council of India for Ethics committee. Subsection 1.4.5 of the Accreditation standards states that monitoring of trials shall be done to ensure equitable selection of subjects, with special attention to vulnerable and high-risk subjects (4). However, there is no matrix to find out whether IEC is able to achieve its objective of patient protection in clinical research.

IECs do passive monitoring by reviewing the continuing review reports, protocol violations, safety reports and completion reports submitted to them by the study team from time to time at regular intervals. However, this form of “passive monitoring” may not portray the real-life scenario of the clinical trial conduct (3,5). Though passive monitoring is done regularly by IEC but, according to the 2017*ICMR Guidelines for Research*, there is a strong need for “active monitoring” as well (6).

Site monitoring procedure is existing in KEM IEC SOP from 14th November 2008 (7).The authors have already done a study to find the EC monitoring practices at KEM hospital from 2008-2010, and found lot of lapses at the site (5). This study was planned as a follow-up to the previous study conducted to analyze the reports of site monitoring visits made by the IECs in the past seven years (2011-2017), and compare the practices now with the past findings from (2008-2010). This paper discusses consequent recommendations made to the investigators as also action taken by the IEC against the study teams.

**Methodology:**

This study was initiated after receiving IEC exemption(IEC(II)OUT/324/17). Twelve clinical studies, both sponsored and investigator initiated, were monitored by the members of the IEC, in the past seven years (2011-2017). The monitoring was done using a standardised format, in accordance with the SOPs of the IEC. The monitoring was routine as well as for cause. The site visits were conducted according to the IEC’s SOP number 12 (7). The Principal Investigators were informed in writing two weeks prior to the scheduled site visits. Their availability as well as their acceptance were confirmed before conducting the site visits. The visiting team consisted of two IEC members, who noted down their observations in their report (Appendix1). Review of documents was conducted in the Ethics Committee Office of the Institute. The Site monitoring forms of the projects, including the initial letter with monitoring findings sent by IEC to the Investigator along with the response by the investigator were reviewed. Later again the 2nd letter by the IEC was also reviewed. The identities of the investigator, sponsor and the monitors of the studies were not noted, and confidentiality was maintained by all the members of the site monitoring teams. The reports were analyzed for violations and categorized under the following themes: 1. Informed Consent issues, 2. Deviation from investigational plan, 3. Non-reporting of study progress to IEC, 4.Deficiencies in study supervision by investigator, 5. IEC approval, 6. Lack of investigator’s understanding about protocol and Informed Consent Document (ICD), 7. Serious adverse event reporting, 8. Other findings: No source documents found; No coded drugs used; Documents not kept under lock and key; Auditors’ monitoring report missing, biodata of investigators in the project file not signed. The study was analysed by descriptive statistics and the findings from the present study were compared with the results of the study conducted by Shetty et al. ~~The χ2 test was used, since the data sets were categorical (binomial).~~

**Results**

Out of the twelve studies monitored in this study, seven were pharmaceutical industry sponsored study while five were investigator initiated clinical studies. The most common violation was seen related to informed consent issues, at 8 out of 12 sites. The other violation themes were lack of investigator’s understanding (6/12), deviation from investigational plan (5/12), non-reporting of study progress to IEC (4/12), patient recruitment prior to IEC approval (2/12). Other violation findings seen in the studies were absence of source documents, improper storage of documents and late reporting of SAE. (Table 1)

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| **Table 1: Violation Themes noted by the Site Monitoring Teams** | | |
| **Sr. No.** | **Violation Themes** | **Monitoring Sites (n=12)** |
| 1 | Informed Consent Issues | 8/12 |
| 2 | Lack of investigator’s understanding about protocol and informed consent document | 6/12 |
| 3 | Deviation from investigational plan | 5/12 |
| 4 | Non-reporting of study progress to IEC | 4/12 |
| 5 | Patient recruitment before IEC Approval | 2/12 |
| 6 | Other findings (5/12):   * No source documents found; * Documents not kept under lock and key; * Principal Investigator (PI) reported SAE late; * Compensation for SAE not paid by sponsor * PI was not eligible to continue in the study as he superannuated and was not a permanent employee of the institute | These issues were noted one in each site |

***Informed consent process***:

Eight of the twelve sites had violation related to the informed consent process. The wrong version of the informed consent document (ICD) was used at one site, which was not approved by the IEC. At one site, there were language errors in the ICD, with over-writing noted in the ICD documents as well. Another issue noted related to informed consent process was the presence of legally acceptable representatives (LAR) signatures in 2 ICDs, along with the signatures of the study participants. In some ICDs, the names of the participants or the investigators were found missing. At one of the sites, the approval date of the translated version of ICD was not found.

One participant at one trial site was interviewed, to assess the participants’ understanding of thestudy. This site was previously advised by the IEC to re-consent based on a previous act of trial consent violation. It was found that the participant had good understanding of the trial after the consenting procedure.

***Lack of investigator’s understanding about protocol***

At six of the twelve study sites, the IEC monitoring teams found that there was a lack of understanding about the study protocol and/or the ICD.

***Deviation from study plan***

Five of the study teams had deviated from the original study plan. Most of the issues were related to the lack of knowledge regarding the proper consenting process, as the monitoring team found ICD related issues in four of these studies. At two sites, the wrong version of the ICD was used for consent procedures, and hence the monitoring team found a need to properly retrain the study team in these cases. One site did not carry out electrocardiogram (ECG) test in 3 patients where cardiac outcome was an area of investigation, thereby leading to possible safety concerns. At the same site, necessary changes were not made in the source documents which were previously ordered by the IEC. At one study site, the study team deviated from the inclusion criteria to recruit patients, thereby leading to a major study violation.

***Non-reporting of study progress to IEC***

At four of the twelve study sites, the monitoring team found that the progress reports were not submitted by the study teams on time.

***Patient recruitment before IEC approval***

At one of the study sites, it was found that 10 participants out of the required 14 were enrolled in the study before the IEC granted a study approval. Similarly, at another study site, it was found that all the required 60 participants were recruited in the study before obtaining an IEC approval. This shows that the study team had a lack of understanding regarding the importance of IEC approval.

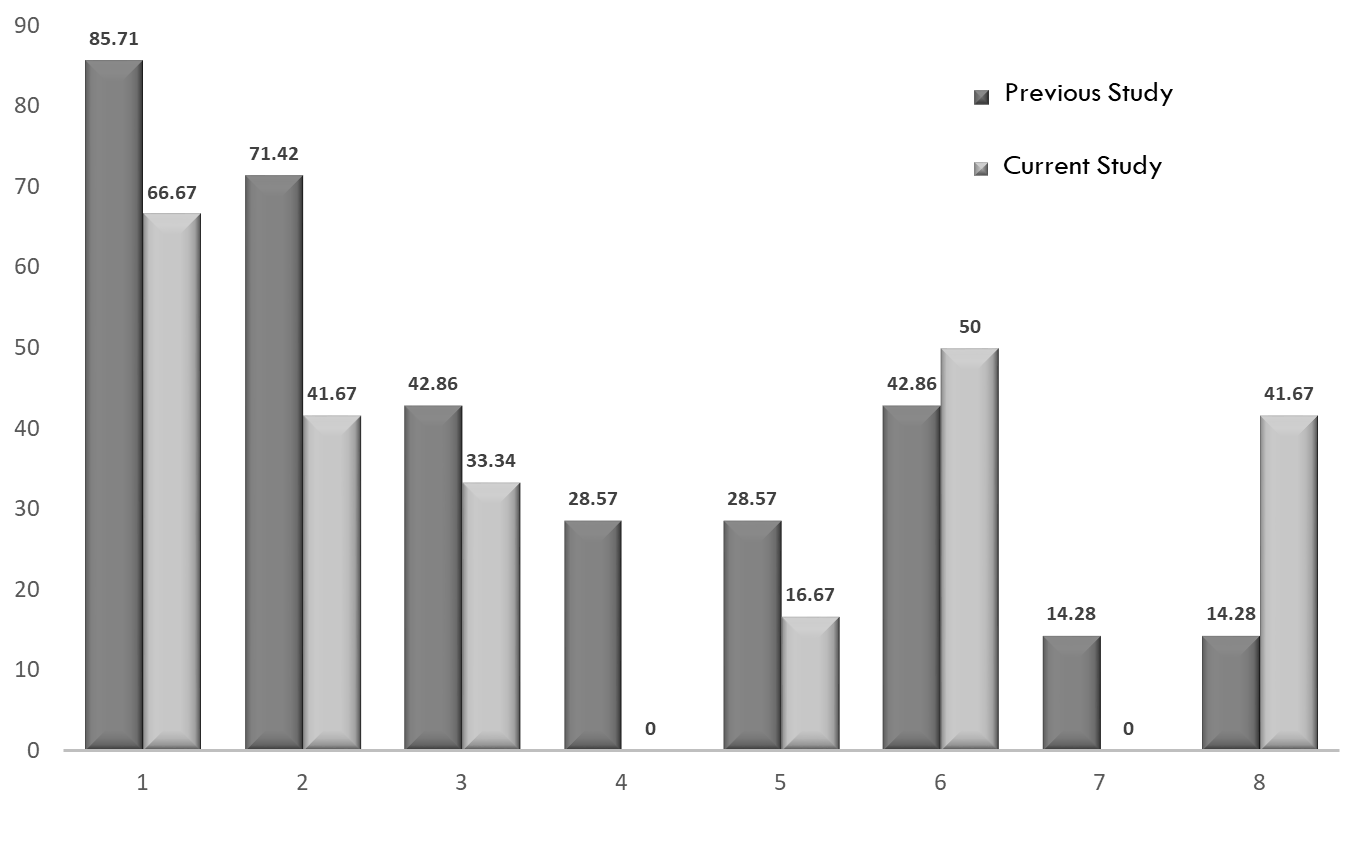
**Other findings:**

Other issues which were reported by the IEC monitoring team at 3 different study sites included absence of source documents at the study site, improper storage of the trial related documents at the study site, late or no reporting of the SAE by the study team and failure to pay compensation to patient for SAE, by the sponsor. In one of the studies, the Principal investigator (PI) was no more permanent employee of the institution, as PI annulment had already happened in May 2015. However, the study was ongoing, but the IEC was not informed about this development. There was no PI oversight in that study.

***Comparison of violation themes observed during site monitoring in2011-2017 with the previous study (2008-2010)***

The most common violation theme in ~~both~~ the current study (2011-2017) and the previous study (2008-2010) was found to be in informed consent. There was an increase in the percentage of cases having issues with investigator’s understanding of the protocol and the ICD in the current study as compared to the previous study (50% vs 42.86%). None of the study sites were found to have deficiencies in the study supervision in the current monitoring ~~audit~~, as compared to the ~~audit~~ monitoring done previously where such deficiencies were found (28.57%). There was an upsurge in some other new violations in the current monitoring ~~audit~~(41.67%) as compared to the previous ~~audit~~ monitoring report . The other findings in the current audit monitoring included lack of source documents at study site, improper storage of the study documents, late reporting of SAE and failure to give compensation to patients who suffered with SAE or AE. ~~However, no statistically significant difference (p = 0.36) was found onχ2 test use, on comparison with the findings of the previous study by Shetty et al~~.Figure 1 depicts the incidence of various violation themes in both the new and the previous monitoring.

**Figure 1: Comparison of Violation themes observed during site monitoring between two studies**



Percentage of studies showing violation

Type of Violation Theme

where, 1. Informed Consent issues, 2. Deviation from investigational plan, 3. Non-reporting of study progress to IEC, 4. Deficiencies in study supervision, 5. Recruitment prior to IEC approval, 6. Lack of investigator’s understanding about protocol and ICD, 7. Serious adverse event reporting, 8. Other findings: No source documents found; No coded drugs used; Documents not kept under lock and key; Auditors’ monitoring report missing; PI reported SAE late; Biodata of investigators in the project file not signed

*~~No statistically significant difference (p = 0.36) was found on χ2 test/Fischer Test use, on comparison with the findings of the previous study by Shetty et al~~*

Actions taken by IEC:

The site monitoring teams prepared and presented their reports atthe next IEC meeting. The findings of the monitoring teams were sent in writing to the PIs of the respective studies, with an instruction ~~appeal~~to establish compliance within one month ~~a period~~. The compliance report was submitted to the IEC andrecommendations were given to the PIs.

In studies where the monitoring team found issues with the informed consenting process or the ICD, reconsenting of the participants was recommended by the IEC. It was also suggested that the re-consented documents be submitted to IEC. At study siteswhere the protocol unawareness was found, the whole team was asked to undergo re-training in protocol as well as GCP. Explanations were asked from the study teams for the protocol deviations and interim reports were asked, to be submitted to IEC on time. At the two sites where recruitment of participants was done before obtaining IEC approval, the twopatient data sets cannot be used in that research and a complete repetition of the enrolment process was recommended. The PI was instructed to make the necessary changes in the source document, wherever needed. The facility at the study sites should be upgraded for proper maintenance of the study documents was one of the recommendations.One of the PIs was asked to pay ~~the~~ compensation to patients, who did late reporting of SAE and did not pay compensation when it was related to study.The PI was also asked to show proofs of the paid compensations to the IEC.

At one of the study sites, the PI was found to have been involved in 5various lapses, in that study as well as in multiple studies before it. The PI was not even a permanent employee of the institution at the time of monitoring visit. The study was ongoing,butthe IEC was not informed about PI retirement.There were many 12 protocol waivers where permission of IEC was not sought , related SAE compensation not paid, number of patients included were more than the approved number.Hence, as per IEC functioning, it was decided that no study protocol will be reviewed by the IEC from that department for next 3 months, and the recruitment procedure for all current ongoing studies from that department would be suspended for 3 months.

The corrective actions taken in this present study and the ones taken in the previous study by Shetty et al have been mentioned in table 2.

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| **Table 2: Corrective Actions in Current Study vs Previous Study5** | |
| Corrective Actions Taken inCurrent Study | Corrective Actions Taken in Previous Study |
| ❖Re-consenting of theparticipants  ❖Explanations asked fordeviations of approved studyplan  ❖The study team was asked toundergo GCP retraining  ❖Interim reports asked to begiven on time  ❖Repeat of participantrecruitmentprocess  ❖Necessary changes in thesource documents  ❖Facility upgradation formaintaining study documents  ❖Compensation to be paid topatients who reported anAE/SAE and show proofs toIEC  ❖In view of multiple lapsesby one of the PI and the site, no protocol to bereviewed from thatdepartment, aspunishment, for 3months and with-holdthe recruitment ofcurrent ongoingstudies | ❖Explanation asked forviolations, with a clearwarning against futureviolation  ❖Audit reports andprogress reports to begiven on time  ❖Recruitment of additionalmembers in the studyteam advised fordeficiencies in studysupervision  ❖AE reports asked to besubmitted on time  ❖Continued GCP trainingof study recommended forthe whole study team |

Discussion:

There were multiple protocol violations reported by the monitoring teams in our study. This was similar to the findings which were found in the study by Shetty et al, which had monitored studies approved by the same two IECs of the same institution. It is important to note that the issues related to informed consent process, deviation from investigational plan, non-reporting of study progress to IEC and recruitment prior to IEC approval were much lesser in the current study as compared to those found in the previous study by Shetty et al, thus indicating better trial execution during 2011 to 2017. Douglass AJ in his study undertaken in New Zealand harps the same finding and insists active on site monitoring to find deviations which cannot be identified passively .8 Ochieng et al.; a study in Uganda has found lapses in informed consent documentation and 25% of the studies ongoing annual updates were not submitted to IEC. They also recommend that on site compliance monitoring could be the most appropriate method to minimize such non-compliance, but is often ignored by the IECs purportedly due to lack of capacity, requires high cost to maintain both in terms of human resource as well as financial resources.Uganda has 14 accredited IECs that review and approve research but only four have reported carrying out monitoring of approved studies at the site and only one was found to have records at the site as evidence for conducting on site compliance monitoring .9 Deficiencies in study supervision, which were found at 28.57% study sites in the previous study by Shetty et al, were totally absent in our current study. This shows that there has been an improvement in the study management and regulationby the sponsor and the investigator over the past few years.

Some new issues were brought forth by the IEC in this studywhilemonitoring clinical trial sites. Absence of source documents were found, improper and unsafe storage of documents was noted, late reporting of SAE and non-payment of compensation for AE were also seen; which were new violation issues when compared to the study by Shetty et al. This shows that there is a need for facilities at trial site to properly store the trial-related documents and to make the study team aware about the importance of reporting and compensating the patients suffering from any AE. The IEC mustcheck the site and the investigator ~~rigorously monitor the investigator site~~ before giving approvals so that such deviations are avoided.

There were a few positive findings which were noted by the site monitoring teams in our study. At one of the study sites, it wasfound that the study team had complied with the recommendations given by the monitoring team on one previous instance. This shows that monitoring of study sites does help in betterment of the trial conduct, and hence they should be done in both the passive and the active form. At another study site, a participant was interviewed in relation to his understanding of that study, and it was found that there was no coercion or lapse in the recruitment procedure in that study. This showed that the study teams may be ethical in their approach towards participant recruitment and trial conduct, however they are involved in ICD related violations more often probably due to the clinical work overload as this are public hospitals.

Despite the few positive findings, the plethora of protocol violations suggests an urgent need for an active monitoringprogramme by the IECs to continue review of ongoingprojects.IECs need to have mechanisms for site monitoring in placeto ensure studies are being conducted incompliance with the protocol, SOPs, regulatoryguidelines and GCP. There are many hurdles for executing active site monitoring, which include lack of infrastructure, manpower, funds and time. One probable solution may be that the IEC can have an internal *monitoring board* for monitoring all fundedand more-than-minimal-risk studies, where no external monitoring is mentioned in protocol. IECs can also train their members to help them monitor clinical trial sites in a better and more efficient way. IEC should take institutional guidance and help ingenerating resources for the same purpose. A study by Smith T etal at Dundee , Scotland had recommended a solution that atleast 10% of projects should undergo on­site review, with all others monitored by questionnaire. They calculated that it requires six person hours of time and a salary bill of £120 per study monitored.. They selected at random a stratified sample of 39 of the 311 projects approved in one year and found similar deviations as our study (10). ICH GCP in its recent guidelines has emphasized on risk based monitoring for the sponsors along with site monitoring .The guidance documents mention about site monitoring , but the mechanisms to be adopted by the IECs has not been detailed (11).So, regulatory studies are monitored by sponsors through Data safety monitoring Boards or regulators also , but academic studies have to be monitored by IEC for oversight . IECs are overburdened because they have to monitor both academic and regulatory studies as the study depicts . Pickworth while mentioning the perspective of USA and Australia, where active monitoring is done by Ethics Committee echoes some of the findings such as of the 39 projects approved , nine were discontinued and only one of these was reported to the committee (3).

Active trial site monitoring helped the IECs to identify the violations which should be tackled. Many of the issues which were encountered were impossible to identify by passive monitoring, hence underlining the importance of the active monitoring. Though our study findings were similar to the ones found by the previous study by Shetty et al, some new issues were noted in our current study which highlights a need for regular active monitoring at study sites in the future as well. This will ensure patient safety and data credibility. But, as there are challenges in setting up an IEC and its smooth functioning ,site monitoring seems to be an herculean task to be fulfilled, but never the less its not impossible as our site has set an example.

The limitations of the current study are it is a retrospective analysis of monitoring reports and corrective actions taken by specific EC. These data cannot be generalized to other setups . As routine monitoring is not a norm for EC, the sites selected for monitoring were majority times for cause.

**Conclusion**:

The study found that active monitoring in different time zones of clinical trials had shown similar violations. So, with proper training and revenue, this can be enhanced to risk-based monitoring for ultimate participant safety and protection.

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