Original Article

Audit of principal investigator's compliance for submission of continue review application and decisions taken on lapses in validity of approval by the Institutional Ethics Committee at tertiary oncology center in Navi Mumbai

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Abstract

Context: A failure to obtain continued Institutional Ethics Committee (IEC) approval for the study before the expiry date assigned by the IEC is considered as "lapse of the IEC approval" to continue the study at the site by the Investigator. Considering this, we had conducted an audit of principal investigators (PI's) compliance for Continuing Review Application (CRA) submission timelines and decision taken on the lapses in the validity of IEC approval continuation.

Aim: The aim of this study is to assess the pre- and post-policy trends of non-compliance management of delayed CRA submission and compare the PI's compliance for submission of CRA between Investigator Initiated trial (IIT) and Pharma studies.

Setting and Design: The present study was a retrospective audit of CRAs of ongoing projects submitted by PIs to IEC, ACTREC.

Materials and Methods: The data from total 199 CRAs submitted for review to the IEC between the year January 2016 and December-2017 were collected and maintained in Microsoft Excel sheet, and later, the data were exported into the SPSS software version 21 for the analysis.

Statistical Analysis: All categorical data were presented in numbers and percentage. The first primary objective was assessed by calculating the duration between the dates of approval for any study to the date of next CRA submission. The CRAs submitted after the project expiry date were considered as a lapse in following the IEC SOP.

Results: This retrospective audit revealed that CRA reminder sent by the IEC to the PI played an important role in compliance w. r. t timely in following the IEC SOPof the CRA by the PI. As a result, overall, 90% of CRAs showed compliance in submitting CRAs to IEC in both IIT and Pharma study. The number of lapses

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were reduced to 7 in the postpolicy period as compared to 15 lapses in the prepolicy period.

Conclusion: This retrospective audit reveals that CRA reminder sent by the IEC to the PI played an important role in improving the compliance of PIs in submitting CRA to IEC. Each IEC should develop the policy to minimize the delays in CRA submission by the PI and prevent lapses in following the IEC SOP.

Keywords: Compliance, Continuing review application, Institutional Ethics Committee, lapses

INTRODUCTION

Ethics Committee (EC) is an entity which is responsible for the protection of the rights, safety and well-being of research participants involved in the clinical trial which is ensured through continuing review of progress of ongoing studies. Post approval, continuing review is a meaningful and substantive evaluation by the Institutional Ethics Committee (IEC) of the conduct of a research project and related documents and events at intervals appropriate to the degree of risk, but not less than once a year.[1]

Continuing review is an important responsibility of the IEC, since it involves the reviewing of the progress of the study, which was previously approved; not only for the changes but to ensure continued protection of the rights and welfare of research participants.[2] The continuing review of these studies is required to occur as long as the research remains active, even when the research is closed for the enrolment of new participants, and all participants have completed all research-related intervention and remains active for long-term follow-up for a period of the study.[3]

It is the responsibility of the principal investigator (PI) to submit the annual status reports to IEC, in a timely manner as mentioned in the EC approval letter. A failure to obtain continued IEC approval for the study before the expiry date assigned by the IEC is considered as "lapse in following the IEC SOP" to continue the study at the site by the Investigator. As per the SOPs of IEC at Tata Memorial Center (TMC), Continuing Review Application (CRA) should be submitted to the IEC at least 60 days before the expiry (or lapse) date and at least annually.[4]

Investigators have to plan in advance to meet required continuing review dates as per the IEC SOPs. If the PI fails to submit CRA to the IEC or the IEC does not approve the continuation of the research, the research must stop. All the research-related procedures such as, participant recruitment or enrolment, collection of data/information, all research-related interventions, or interactions with currently enrolled participants and data analyses involving subject identifiable data must stop.[4]

The review article by Shetty *et al*. emphasizes the importance of continued review and monitoring for ascertaining the ethical conduct of clinical research. Continued monitoring and timely project reviews by IRBs ascertain the ethical conduct of research.[5] An intensive literature review revealed that there are no studies conducted to evaluate the PI's compliance for the submission of the CRA and the proportion of CRA reminders required by the PI between academic and Pharma studies and also action taken by IEC on the noncompliance of CRA submission for the review.

Considering the importance of CRA submission timelines, TMC IEC has made the policy regarding the management of noncompliance with respect to CRA submission timelines and IEC action in March 2017. It is interesting to know that, the compliance rate for the timely submission of CRA to the IEC before and after the policy decision was made by the IEC (2017). The present study was a retrospective audit and aimed to assess the pre and post policy trends of non-compliance management of delayed CRA submission and compare the PI's compliance for submission of CRA between Investigator Initiated trial (IIT/academic) and Pharma studies and to review the IEC decisions on CRA and in case of lapses of IEC approval.

MATERIALS AND METHODS

This study was a retrospective review of CRAs submitted by PIs to IEC. The authors reviewed all CRA reports of ongoing projects retrieved from the electronic database which were approved by TMC IEC-III between the years January 2016 and December-2017. We have also reviewed the CRA reminder registers, IEC agenda and minutes for the review of IEC decisions on CRA and lapses in following the IEC SOP.

Development of data collection tool

We collected the data by retrieving all CRAs submitted for review to the IEC between the year January 2016 and December-2017, and the data were maintained in Microsoft Excel sheet. In the next step, data from the excel sheet were exported into SPSS Statistical Package for the Social Sciences version 21.0 (SPSS, Inc.; Chicago, IL, USA) for Windows. for the analysis.

To compare the trends of noncompliance management in the protocol w.r.t delayed CRA submission, we divided the data into two sets, i.e., the pre and post policy. Considering the importance of CRA submission timelines, IEC at TMC has developed the policy regarding the management of noncompliance with respect to lapse in following the IEC SOP and IEC action in March 2017. As per the policy, IEC secretariat has to send the first CRA reminder to the PI, 90 days followed by 60 days in advance before the project expiry (or lapse) date. If, IEC does not receive any CRA or no response from the PI after two reminders, IEC will issue warning letter to the PI and take appropriate action after discussing in the full board meeting. The prepolicy data included CRA received between January 2016 and February 2017 and the postpolicy data included CRA received from March 2017 to December 2017.

Ethical consideration

The current study was undertaken after seeking the approval by IEC of TMC ACTREC. The CRA details and/IEC responses were kept anonymous by coding and identification numbers which were kept confidential while publishing the study.

Data analysis and statistical consideration

Data analysis was carried out by using the SPSS software version 21. The first primary objective was assessed by calculating the duration between the dates of approval for any study to the date of next CRA submission. The CRAs submitted after the project expiry date were considered as lapse in following the IEC SOP. The number of reminders sent to PI prior to the CRA submission were recorded for each study. All categorical data were presented in numbers and percentage.

RESULTS

A total of 199 CRA reports from 121 studies submitted during January 2016–December 2017 were included in the final analysis. Out of 121 studies, 114 (94%) were IIT and 7 (6%) studies were Pharma Sponsored studies [Figure 1a]. The nature of 68 (56%) studies were basic sciences, 24 (20%) studies were Clinical Interventional and 29 (24%) studies were Clinical NonInterventional [Figure 1b].

The investigator analyzed the number of reminders required to submit CRA by the PI per study type [Figure 1c], it was observed that in IIT studies, out of 188 CRAs, 108 (57%) required 1 reminder, whereas 49 (26%) required two reminders, 21 (10%) required 3 reminders, 8 (4% CRAs were requiring more than three reminders to submit CRA, while out of 11 CRAs in Pharma Sponsored studies, 5 (45%) required 1 reminder, 4 (36%) studies required 2 reminders, and for 2 (18%) 3 reminders were required to submit CRAs.

As shown in Figure 1d, out of 199 CRAs, the status of the studies were 26 (13%) had completed accrual, 117 (59%) were on active enrolment, 36 (18%) were follow-up ongoing, trials, whereas 20 (10%) of them were not initiated yet.

Table 1 shows the types of reminders required to submit CRA and PI's response on reminder**.** Out of 188 IIT studies, 176 (94%) studies had reminders sent through E-mail, whereas 10 (5%) reminders were given verbal as well as electronic sent through E-mail. 2 (1%) no reminder was sent by IEC as CRA was received beforehand.

In IIT studies, 11 (6%) PI had responded to CRA reminder sent by IEC, whereas in 175 (94%), PI did not respond to CRA reminder sent by IEC. In pharma studies, 2 (18%) PI had responded to CRA reminder sent by IEC, whereas 9 (82%) PI did not respond to CRA reminder sent by IEC.

Institutional Ethics Committee decision on continue review application

As shown in Figure 2, we evaluated the distribution of IEC decision on CRA in IIT and Pharma Sponsored Studies, it was observed that, out of 188 CRAs in IIT, 42% (n = 79) CRAs were approved with the extension of validity, 36% (n = 68) CRAs were approved, for 19% (n = 35) CRAs IEC had sent query and 3% (n = 6) CRAs were not approved. Out of 11 CRAs in pharma studies, 64% (n = 7) CRAs were approved with the extension of validity, 9% (n = 1) CRAs were approved, and IEC had sent query in 27% (n = 3) CRAs.

We evaluated the PI's compliance regarding the submission of CRA between IITs and Pharma Sponsored Study which was depicted in Figure 3a. It was observed that, out of 188 CRAs in IIT, 167 (89%) showed compliance. Out of 11

Table 1: Types of reminders required to submit continue review application

	Trial initiated by (%)	
	Investigator initiated trial (n=188)	Pharma (n=11)
Type of reminder sent		
E-mail	176 (94)	11 (100)
E-mail + verbal	10 (5)	0
Reminder not sent	2 (1)	0
Principal investigators response on reminder		
No	175 (94)	9 (82)
Yes	11 (6)	2 (18)

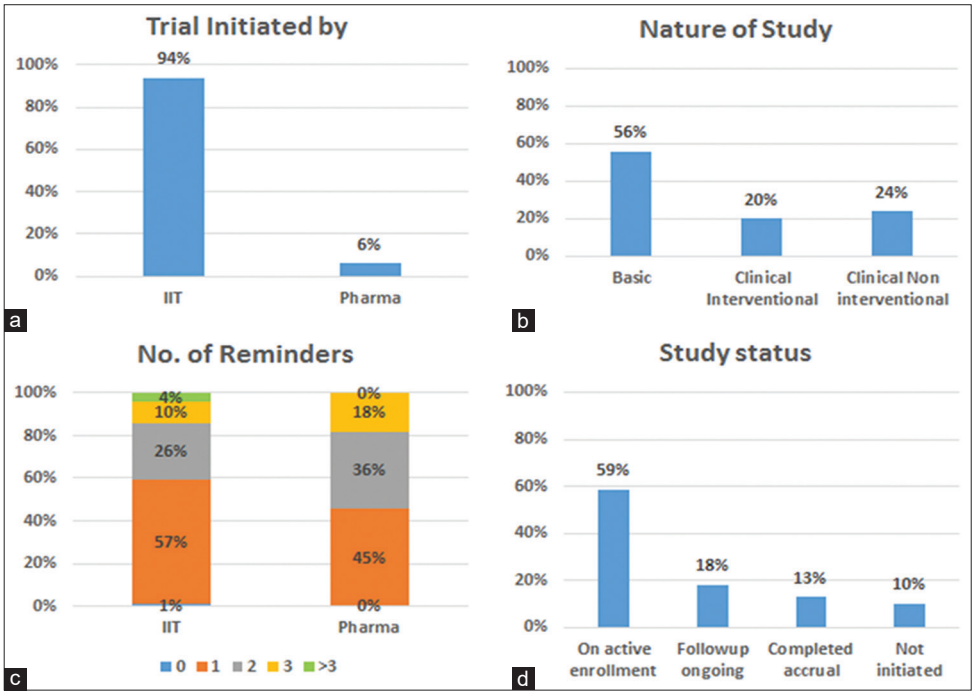

Figure 1: Characteristics of Continuing Review Application received for studies. (a) Represents the Continuing Review Application received per study type (*n* = 121). (b) Represents the distribution of Continuing Review Application received per nature of study (*n* = 121). (c) Represents the frequency of reminders required by the PI between Investigator Initiated trial and Pharma (*n* = 199). (d) Represents status of the study for which Continuing Review Application received (*n* = 199)

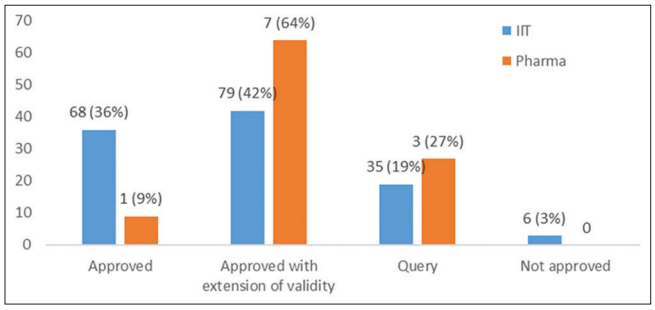

Figure 2: Types of Institutional Ethics Committee decision on Continuing Review Application (*n* = 199)

CRAs in Pharma, 10 (91%) CRAs showed compliance. Both types of studies had the similar patterns of CRA submission.

As shown in Figure 3b, we analyzed the lapses in the submitted CRA by the PI and action taken by the IEC in case of lapses in the IEC approval in the pre- and postpolicy period. There were 15 delayed CRAs and 7 delayed CRAs were found in the prepolicy period and the postpolicy period, respectively.

It was found that in 5 (33%) delayed CRAs out of 15 IEC has reprimanded the "PI with instruction to ensure IEC stipulated time lines to submit ASR/CRA in the future" in prepolicy period, in 2 (13%) delayed CRAs, IEC has requested the PI to submit a deviation report to the IEC and in 1 (7%) delayed CRAs, IEC has closed the study.

In postpolicy period, out of 7, IEC instructed the "PI to ensure IEC stipulated time lines to submit ASR/CRA in the future" in 3 (43%) delayed CRAs and IEC has instructed the PI to submit a new proposal in 2 (29%) delayed CRAs.

No action taken by IEC in case of lapses were 7 (47%) in prepolicy period, which was reduced to 2 (29%) in the postpolicy period as the number of lapses was decreased in the postpolicy period.

As shown in Figure 4, the most common deficiency/query raised during the CRA review, it was observed that 39% were discrepancies in the CRA form, 23% were slow accrual in the study, and 14% were errors noted in the utilization of the budget. IEC recommended to submit a study closure report and to submit a protocol deviation and violation in 7% CRA review each. IEC recommended suspension of the study in 2% CRA and PI to resubmit CRA and consent related issues in 2% CRA review.

DISCUSSION

This retrospective audit revealed that overall 90% had no lapses found in submitting CRAs in both IIT and Pharma sponsored studies which suggests that investigators are more compliant with regard to timely submission of CRA to IEC. The investigators should plan ahead of time to ensure the continuing review of the research before the

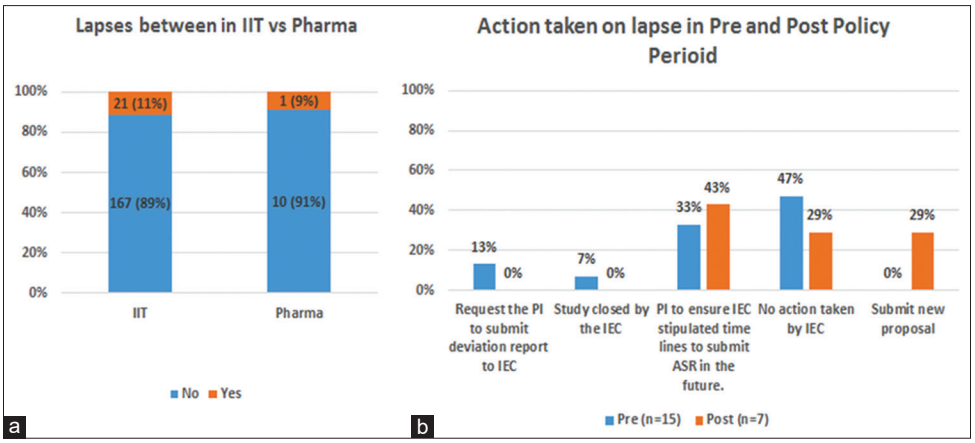

Figure 3: (a) Represents the percentage of PI's compliance for submission of Continuing Review Application lapses observed between Investigator Initiated trial and Pharma (b) represents the action taken on lapses in Pre and Post policy period

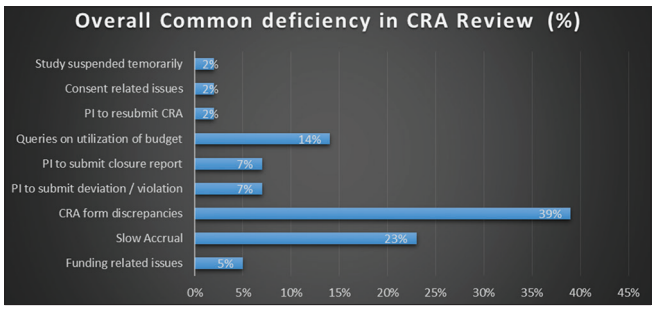

Figure 4: Most common deficiency/errors in Continuing Review Application review

validity of the study expires.[6] In practice, TMC IEC is also mandating the investigators to submit the CRA annually by mentioning the date in the final approval letter to ensure that CRA or completion report is submitted to IEC before the expiry date to prevent the lapse of IEC approval. TMC IEC have computerized tracking system in place for sending CRA reminders to minimize any unintended expiration of IEC approval.

One of the significant finding in our study was that CRA reminder sent by the IEC to the PI played an important role in compliance w. r. t timely submission of the CRA by the PI. As a result, overall, 90% of CRAs showed compliance in submitting CRAs to IEC in both IIT and Pharma study. The multiple number of reminders required in investigator initiated studies shows that PIs are more dependent on IEC reminders to submit CRA on time.

Investigator has compared the trends of noncompliance management in the protocol w. r. t delayed CRA submission between the pre- and postpolicy period. This audit revealed that there were 15 delayed CRAs and 7 delayed CRAs were found in the prepolicy and postpolicy period resp. which suggests that there is improvement in the rate of lapses in IEC approval by the PI after the policy has been implemented compared to the pre policy period. The findings of the study suggested that, each IEC should develop the policy to minimize the delayed CRA submission by the PI and prevent lapses in following the IEC SOP. The policy adopted by the TMC IEC was congruent with the UIC Office for the Protection of Research subjects policy for lapse in IEC approval.[7]

For the last two decades, the lapse in IRB Continuing review is one of the most common noncompliant findings, according to FDA and GAO reports.[8,9] In our study, it was noticed that overall 11% lapses occurred in total 199 CRAs. Out of total 22 lapses found in submitting CRA, the majority of lapses were found in IIT studies (21; 11%) as compared to Pharma sponsored studies (01; 9%). TMC IEC has taken corrective steps by implementing the actions on the delayed CRA submission. In the majority of lapses, IEC has reprimanded the PI with instruction to ensure IEC stipulated time lines to submit CRA in the future" and also requested the PI to submit a deviation report for delayed CRA submission and in one case IEC has suspended the study. In the postpolicy period IEC has instructed the PI to submit a new proposal in 2 (29%) delayed CRAs.

The investigator has also studied the types of IEC decision on CRA in IIT and Pharma Sponsored Studies. One of the interesting findings of this study was that out of 188 CRAs in IIT, 6 CRAs (3%) were not approved by the IEC. The reasons for not approving the CRAs were lacking detailed study progress report as per the study objectives in one case. In another project, IEC recommended the monitoring of the project after receipt of the CRA which was scheduled before discussing the CRA in the full board. During the monitoring visit, monitors identified, violation of the Protocol as PI had accrued more subjects than the

target approval set in the protocol, In another case, study suspended temporarily due to pending submission of final MOU and IEC recommended monitoring of the project. In one case, PI had added one new objective along with the funding request; hence, IEC suggested PI to submit complete the project and to submit a new project for additional objectives with funding request and these studies were biomedical studies in nature.

In our study, while investigating the most common queries raised during the CRA review, it was observed that the majority (39%) of discrepancies were found in the CRA form. The various CRA form discrepancies observed were submission of incomplete and poor quality progress report, typo errors in the summary of the participant's section on the CRA form, failure to notify the deletion of Co-I while submitting the CRA, etc., This emphasized the need for conducting in house training by the IEC for investigators on the submission of CRA. The second most common query raised during the CRA review was slow accrual (23%) in the study. In order to overcome the slow accrual, investigators and CRCs need to be sensitised clinicians or coinvestigators for sending the eligible patients to the respective investigators to expedite the accrual.

Our study was limited by the fact that we evaluated only the PI's compliance for submission of CRA and the review of IEC decisions on lapses in IEC approval. However, we did not assess how frequently investigators continued research activities during the lapse. The meta analysis conducted by Min-Fu Tsan on IRB Continuing Reviews revealed that lapse in IRB continuing reviews was the most commonly identified noncompliance.[6] However, investigators from <3% of lapsed protocols continued research activities during the lapse.

CONCLUSION

This retrospective audit reveals that CRA reminder sent by the IEC to the PI played important role in improving compliance of PIs in submitting CRA to IEC. Each IEC should develop the policy to minimize delays in CRA submission by the PI and prevent lapses in following the IEC SOP. Future studies may focus on studies which continued patient accrual pending ECs continued approval.

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Conflicts of interest

There are no conflicts of interest.

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