Original Article

Post-approval process: A challenge for ethics committees

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Abstract

Context: Ethics committees (ECs) work toward upholding rights, dignity, safety, and well-being of research participants. They are also tasked with conducting oversight pre- and post-approval. ECs face various challenges in their functioning. Post-approval oversight is one of the major challenges, and various studies have stressed the importance of post-approval oversight.

Aims: The aim of this study was to explore the challenges in the post-approval processes that are faced by the ECs and to suggest solutions to the most common challenges.

Methods: We conducted a quantitative study contacting member secretaries of different ECs using an online Google Forms questionnaire. The questionnaire consisted of three domains and included questions about the description of the EC, conduct of post-approval activities, and challenges encountered during the post-approval process.

Results and Conclusion: We received responses from 61 member secretaries. We were able to identify challenges faced by the EC members in the post-approval process in the areas of site monitoring visit, review of post-approval submission (nonsubmission/incomplete submission/late submission of documents by PI, long time taken by reviewers, nonavailability of reviewers, nonadherence to timeline and too much paperwork), review of serious adverse events, and review of protocol deviations. Our study also noted the difference between accredited/assessed (National Accreditation Board for Hospitals and Healthcare Providers/ Forum for Ethical Review Committees in the Asian and Western Pacific Region) ECs versus registered (Central Drugs Standard Control Organisation/Department of Health Research only) ECs by comparing the challenges.

Keywords: Challenges, ethics committees, follow-up, post-approval process, review

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INTRODUCTION

The earlier scandals and the exposure of Tuskegee study led to the development of Belmont report and stressed the requirement of the ethics committee (EC) to review protocols.[1] The importance of review was further promoted by the Council for International Organizations of Medical Sciences guidelines.[2] Thus, the role review boards gained importance in 1975, and has become the golden rule for conduct of human subject research to undergo a robust review process before initiation.[3]

Thus, the institutional review boards and the EC work toward evaluating research projects. In India under the Central Licensing Authority, the Central Drugs Standard Control Organisation (CDSCO), 1483 are

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re-registered, whereas under the Department of Health Research (DHR), 719 are provisionally registered and 108 are registered. Similarly, 185 have accreditation from the National Accreditation Board for Hospitals and Healthcare Providers (NABH) and 17 are assessed from the Forum for Ethical Review Committees in the Asian and Western Pacific Region (FERCAP);[4-7] CDSCO and DHR are involved in registration of ECs at national level whereas NABH is a national agency involved in accreditation and FERCAP is an international agency involved in assessment.

Besides robust initial review, ECs are also tasked with continuous review of projects after approval[3] known as post-approval review. Huge efforts are being put in the preapproval process, but it severely lacks tracking and oversight post-approval.[3]

The continuing review is necessary to ensure the ethical conduct of research. However, ECs in India have neither the mechanisms in place nor the manpower or resources to meet this requirement and therefore cannot fulfill this obligation.[8] Thus, challenges faced by EC/IRB members in this context form the background for the study.

METHODS

Institutional EC approval was obtained before initiation of the study. The study involved an online questionnaire to be answered by the Member Secretary of the ECs via Google Forms to explore the challenges in the post-approval processes and suggest solutions to the most common challenges. It consisted of 15 questions under three domains, about the EC, about the post-approval/follow-up functioning of the EC and challenges faced during post-approval/follow-up functioning of the EC. The tool included a question to allocate an overall score with respect to conduct of post-approval activities by EC (0 referring to none and 5 referring to adequate). The sample size was calculated to be 60 with 5% level of significance and 85% power. The Google Forms was sent to more than 350 E-mail IDs and participant information sheet and informed consent form were attached with the Google Forms and consent was obtained and responses were collated.

Further percentage analysis was done for each variable and comparison analysis was done for accredited/assessed (NABH/FERCAP) versus registered (CDSCO/DHR only) ECs.

RESULTS

Responses obtained from 61 member secretaries indicated 61 ECs representing 18 states across India. More than 90% of these participating ECs were registered under the CDSCO. More than 67% were registered under DHR. Half of the ECs had also attained quality accreditation, most of which were accredited by NABH and few <10%, by FERCAP.

2–4 years was found to be the highest average number of experience as member secretary in the EC and all participating ECs were involved in conducting post-approval activities.

Post-approval/follow-up functioning of the ethics committee

Most ECs review amended protocols, protocol deviations (PDs), and completion reports. More than two-thirds of the ECs conduct continuing review of protocols, site monitoring, and serious adverse event (SAE) review and more than half of the ECs review publications.

Most member secretaries have participated in conducting post-approval activities, which include continuing review of protocols, review of amendments, and completion reports. About two-thirds of them participated in site monitoring, review of SAE, and PDs and more than half of them reviewed publications. With respect to member secretaries' views on layperson's participation in post-approval activities, about two-thirds agreed with the layperson's participation in reviewing amendments of protocols, continuing review, completion reports, SAE, and PDs. Nearly half agreed with their participation in site monitoring while two-thirds disagreed with the layperson's participation in reviewing publications. Regarding the views on external member's participation, it was observed that two-thirds agreed with external representative's participation in reviewing amendments, completion reports, continuing review of protocol, SAE, and PDs. About half of them agreed with external representative's participation in site monitoring and review of publications.

About half of the member secretaries agreed the reason to conduct post-approval activities when it is suggested by few members in EC or when it is a requirement by the institution or by NABH. More than two-third agreed involvement of the whole EC, while most agreed the role of Standard Operating Procedure (SOP) and Indian Council of Medical Research (ICMR) requirements to conduct post-approval activities.

Challenges faced during post-approval/follow-up functioning of the ethics committee

With regard to post-approval submissions, most ECs face nonsubmission/incomplete submission of protocol

documents as challenging. About two-thirds of the member secretaries agreed late submission, nonavailability of reviewers, nonadherence to timelines and too much paperwork as challenges in the review of post-approval submissions while of half them agreed long time taken by reviewers as one of the challenges.

Regarding the conduct of site monitoring visit (SMV) half of the member secretaries agreed to nonavailability of EC members and time and more than one-third accepted noncooperation of researchers, and lack of training while 21% agreed noncooperation by the institute as a challenge in conduct of SMV.

Regarding SAE review, about half of the member secretaries agreed to nonsubmission/incomplete/late submission of SAE reports by PI, more time taken for review, too much paperwork work, establishing causality, and deciding compensation as challenges. About one-third acceded nonavailability of reviewers, nonadherence to timeline, lack of expertise, and strict rules in reporting SAE to Drugs Controller General of India as challenges in reviewing SAE [Figure 1].

With respect to the review of PDs, more than two-thirds of the member secretaries agreed noncompliance by Principal Investigator (PIs) in reporting PD, and about half agreed that PIs do not accept PDs and unavailability of time to detect PDs. One-third agreed lack of clear SOP and EC's inability to take action against PI and one-fifth mentioned lack of institutional support as challenges in review of PDs [Figure 2].

The overall score for conduct of post-approval activities by EC such as availability of time, dedication by EC members, leadership of chair/Member Secretary (MS), support by institute, secretarial support, clearly written SOPs, checklist, training of EC members, support by researchers, and digital presence (where 0 refers to none and 5 refers to adequate) was collated and the mean score was identified to be above 3 except for digital presence.

Comparison of challenges faced by ethics committees

As we received participation of 30 (only registered ECs) versus 31 (NABH/FERCAP assessed ECs), we did a comparison and observed differences in six areas with respect to challenges faced by EC in the review of post-approval submissions, which include nonsubmission/incomplete/late submission of documents by PI, long time taken by reviewers to review post-approval documents, nonavailability of reviewers, and nonadherence to timelines [Figure 3].

With respect to comparison of challenges faced by EC in conduct of SMV and SAE review, no major differences were observed, except a difference was observed with respect to strict rules in reporting SAE to the drug controller, with 33% of registered ECs agreeing it as a challenge while 45% of accredited/assessed ECs agreed.

With respect to comparison of challenges faced by EC in review of PDs, differences were observed with respect to noncompliance in reporting of deviations by PI, nonacceptance of deviations by PI, nonavailability of time to detect PD, lack of clear SOP for PD, EC's inability to take action against PI, and lack of institutional support in detection of PDs [Figure 4].

To mitigate the challenges identified in the post-approval process, some solutions were suggested by the participating

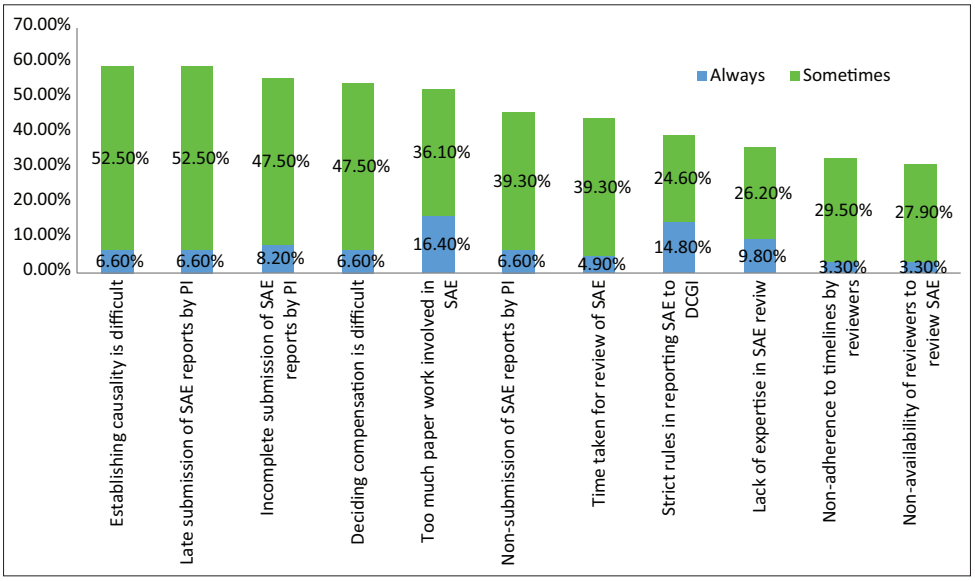

Figure 1: Challenges faced by EC in the SAE review. EC = Ethics committees, SAE = Serious adverse event

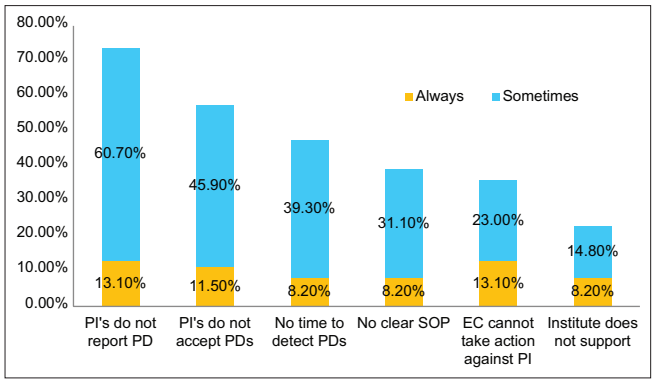

Figure 2: Challenges faced by EC in the review of PDs. EC: Ethics committees, PD: Protocol deviations, PI = Principal Investigator

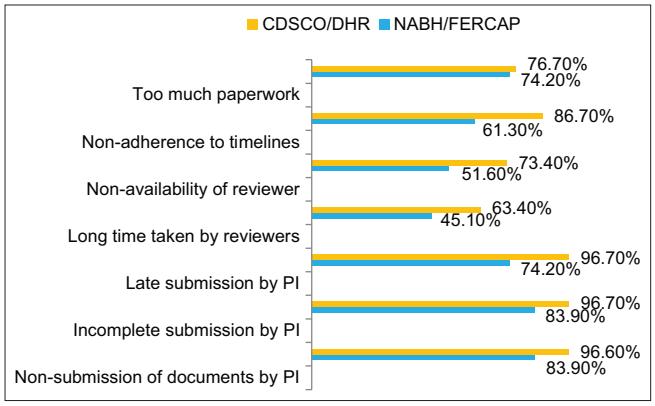

Figure 3: Comparison of challenges faced by EC in the review of post-approval submissions. EC = Ethics committees, CDSCO = Central Drugs Standard Control Organisation, DHR: Department of Health Research, NABH = National Accreditation Board for Hospitals and Healthcare Providers, FERCAP: Forum for Ethical Review Committees in the Asian and Western Pacific Region

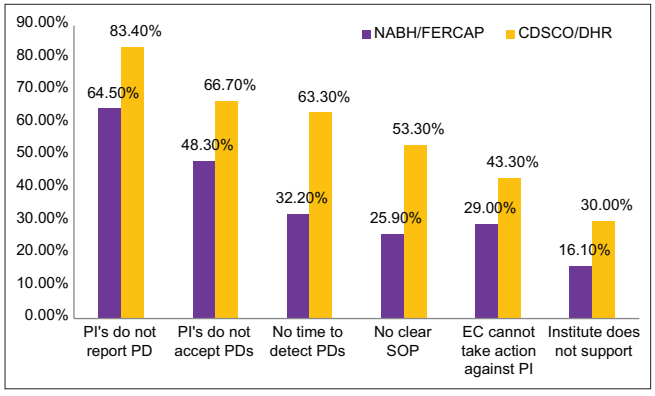

Figure 4: Comparison of challenges faced by EC in review of protocol deviations. EC = Ethics committees, PD = Protocol deviations, PI = Post-Approval Activities, DHR = Department of Health Research, CDSCO = Central Drugs Standard Control Organisation, FERCAP = Forum for Ethical Review Committees in the Asian and Western Pacific Region, NABH = National Accreditation Board for Hospitals and Healthcare Providers

member secretaries. These include regular training of EC focusing post-approval oversight, awareness of SOP, need for robust and increase in secretariat staff/clinical assistant, need for compensation for time devoted by EC/ to be recognized as full-time job status, and incorporation of automated digital platform system for tracking and scheduling oversight with data protection.

DISCUSSION

A review of literature brought out deficiency in monitoring which contradicts the requirement as per ICMR 2017 guidelines stating "*ECs have a continuing responsibility to regularly monitor the approved research to ensure ethical compliance*" and our results also pointed the need for strengthening the monitoring system as one of the post-approval activities. In the present study, more than one-third (37.7%) of member secretaries did not participate in site monitoring, more than half (54%) agreed that lay representatives do not participate in site monitoring, and more than 1/3 (41%) denied participation of external members in SMV, which mirror the views of inadequacy in monitoring highlighted by Kuyare *et al.*, 2014; Thatte and Marathe, 2017; and Shafiq *et al.*, 2020.[9-11]

Other challenges associated with site monitoring were found to be non-availability of members, non-availability of time as agreed by half of the member secretaries and more than one third acceded lack of training to conduct SMV, as challenge and thus reflecting the views of Shetty *et al.*, 2012; Kuyare *et al.*, 2014; Thatte *et al.*, 2017; Davis, 2018; Bediako *et al.*, 2020.[8-10,12,13]

The present study highlights that most participating ECs face nonsubmission of protocol documents as a challenge in the review of post-approval submissions as described by Bhatt, 2012, and Sambiéni, 2018,[14,15] and also cited by Das and Sil, 2017.[16] Other challenges associated with post-approval submission in the current study were found to be incomplete submission, late submission of documents by PI, long time taken by reviewers, nonavailability of reviewers, and nonadherence to timelines. In addition, present study also highlights excessive paperwork as a challenge which reflects heavy workload, administrative burden and thus mirroring the views of Kandhari, 2013; Sambieni, 2018;Bediako *et al.*, 2020 and Shetty *et al.*, 2021.[3,13,15,17]

Regarding continuing review, the present study highlights that more than two-thirds of the member secretaries agreed their ECs participation in continuing review of protocols while one-sixth conduct sometimes and 7 denied participation. More than half of the member secretaries agreed to lay representatives' participation in continuing

review of protocols while one-sixth mentioned sometimes while nearly one-third disagreed. Two-thirds agreed with external representatives' participation in continuing review of protocols with 8 members performing sometimes and 14 disagreed with their participation. It shows inadequacy with respect to participation by nonmedical members as described by Kandhari, 2013,[3] but contradicts the view of Sambiéni, 2018, as complete failure in conducting continuing review.[15]

Further, the present study indicates under-reporting or nonsubmission of SAE reports by PI as nearly half of the member secretaries agreed nonsubmission of SAE reports by PI as a challenge in reviewing SAE, which was similar to observations reported by Shafiq *et al.*, 2020; Jalgaonkar *et al.*, 2016; Bhatt, 2012; and Das and Sil, 2017.[11,14,16,18] and further contradicts the requirement laid by Good Clinical Practices guidelines stating "The investigator should promptly report to the ethics committee, deviations, all adverse drug reactions and adverse events that are serious and/or unexpected." Other issues associated with SAE reporting were identified to be a late submission of SAE reports similar to findings observed in some studies. More than half of the member secretaries referred deciding compensation as challenging which mirrored the views of Kuyare *et al.*, 2014, in their review article.[9] The authors of the present study believe that experienced trained past EC members can be roped in with necessary amendments in SOPs and signing of privacy confidentiality documents to review specific functions like SAE and help the overburdened EC. The reasons for safety concerns with respect to SAE under-reporting/delayed reporting by PI need to be explored. It can be due to lack of awareness of the protocol or safety guidelines for reporting SAE. Similarly, inability of EC to do causality assessment and timely review can be due to heavy workload and lack of training. Such systemic issues can impinge on patient data and need to be addressed on a serious note.

In addition to underreporting of SAE, underreporting of PDs was also identified as a challenge in the present study, which was also highlighted in studies done by Jalgaonkar *et al.*, 2016, and Davis *et al.*, 2018.[12,18] More than one-third of the member secretaries agreed lack of clear SOP as a challenge to review PD. The authors are of the opinion that lack of clear SOP adds to the challenge in reporting of PDs due to lack of clarity with regard to timeframe for reporting, corrective actions to be taken, and further whether those actions were implemented or not.

Moreover, Page, 2017, highlighted lack of institutional support for EC functions;[19] on the contrary, our study identified that more than half of the members agreed involvement of the institute as one of the reasons to conduct post-approval activities and a satisfactory score for institutional support was found to be 3.98 out of 5. However, 23% of member secretaries agreed lack of institutional support as a challenge in review of PD and 21% agreed noncooperation by the institute as a challenge for site monitoring.

It was interesting to observe that accredited/assessed (NABH/FERCAP) ECs found activities such as nonsubmission/incomplete submission/late submission of documents by PI, long time taken by reviewers, nonavailability of reviewers, nonadherence to timelines, noncompliance in reporting PDs, nonacceptance of deviations by PI, nonavailability of time to detect PD, lack of clear SOP for PD, EC's inability to take action against PI, and lack of institutional support to detect PD as less challenging as compared to (only CDSCO/DHR) registered ECs. Regarding comparison of challenges faced by EC in conduct of SMV and SAE review among accredited/assessed ECs versus only registered ECs, no major differences were observed, except with respect to strict rules in reporting SAE to the drug controller. It could be possible that since non-accredited ECs often do not review SAE, it might have been reported as less challenging by the respondents as compared to accredited/assessed ECs.

These findings highlight that accreditation helps in improving function as they have system in place which further reflects improvement in quality as also found in a study conducted by Desai *et al.*, 2017,[20] and quoted by Bhatt, 2017, in his article that "accreditation is expected to improve quality and capacity of ECs,"[21] and in our study, it was found. However, the author also mentioned, "ECs will need knowledge, resources, manpower, funds, time, planning and commitment from management and guidance from experienced ECs."[21]

Mandatory CDSCO registration and changes in regulations have "empowered" EC functioning[22] and streamlined the processes. While functioning is improved, ECs are still burdened with more work and post-approval follow-up needs more attention.

In addition to the challenges identified, many solutions were suggested by the participants. These include regular training of EC focusing post-approval oversight which was also highlighted in the literature review as need for training and capacity building by Shetty *et al.*, 2012; Kuyare *et al.*, 2014; Page and Nyeboer, 2017; Davis *et al.*, 2017;

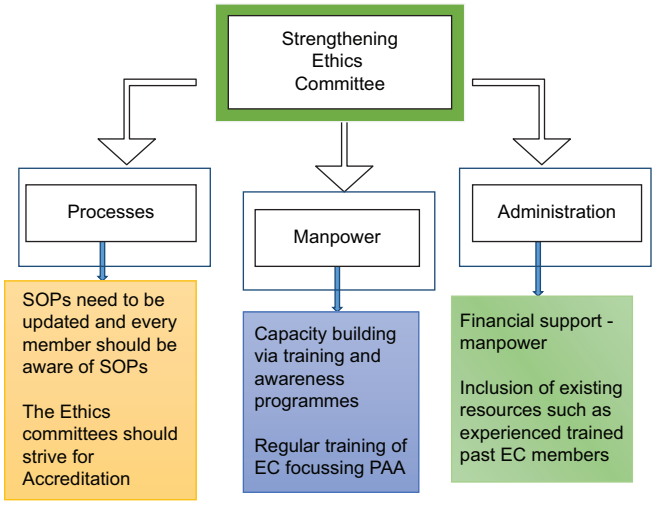

Figure 5: Recommendations. EC = Ethics committees, SOP = Standard operating procedure, PAA = Post-Approval Activities

and Davis *et al.,* 2018.[8,9,12,19,22] The need for robust and increase in secretariat staff/clinical assistant as suggested by participants was highlighted by Apau Bediako and Kaposy, 2020, and Page and Nyeboer, 2017, as the need to increase manpower.[13,19] The need for compensation for time devoted by EC to be recognized as full-time job status as suggested by participants was stressed by Kuyare *et al.*, 2014, and Apau Bediako and Kaposy, 2020, as need for financial support for EC functioning.[9,13] Incorporation of automated digital platform systems for tracking and scheduling oversight with data protection as suggested by participants in the current study was also stressed by Brown *et al.*, 2014.[23]

CONCLUSION

Post-approval activities play a very crucial role to ascertain participants' rights, safety, and well-being. We were able to identify challenges faced by the ethics committee members in the areas of review of post-approval submissions, conduct of site monitoring visit (SMV), review of serious adverse events (SAE), and review of protocol deviations (PD).

Our study also noted the difference between accredited/assessed ECs vis-a vis only registered ECs by comparing the challenges and observed, accreditation/assessment improves the Post-approval process because of structured SOPs and adherence to the processes. Since accreditation/assessment procedure demands leadership from the institute, the process is sustained.

Recommendations

As the second objective was to suggest solutions to the most common challenges, we have recommendations under three headings to make the ECs more efficient in functioning and resilient to the increasing burden: first being "Processes" which stresses on the need to update SOPs, its awareness among members, striving for accreditation, and conduct of internal audits to adjust to the evolving changes; second being "manpower" and capacity building of ECs and stakeholders involved in research through training concerning document submission, reporting, and regular training of EC members focusing post-approval activities; and third being "Administration" by providing financial support to meet the increasing demand of manpower. To deal with excessive workload, we suggest inclusion of existing resources such as past experienced/trained EC members can be roped to review specific functions of overburdened EC with necessary amendments in SOPs and signing of privacy and confidentiality agreement [Figure 5]. Improvement in post-approval monitoring can be achieved by making investment in technology and incorporating digital presence for review of research-related documents with data protection.

Limitations

Being a quantitative study, it lacks the insight on particular responses if conducted as a mixed method.

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Conflicts of interest

There are no conflicts of interest.

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