Original Article

Ethics committees and the changed clinical research environment in India in 2016: A perspective!

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Abstract

Introduction: Institutional and Independent Ethics Committees (ECs) have as their primary mission the protection of human research subjects. The Central Drugs Standard Control Organization has in the period 2013–2016 introduced several new regulations and amendments to existing regulations overseeing the conduct of Research in India. Several of these have direct effect on the functioning of the EC from a review, approval, and oversight mechanism.

Methodology: The Ethics Council of Indian Society for Clinical Research conducted a questionnaire survey among EC members to understand the impact of these changes in their functioning. The domains surveyed included awareness about recent changes/amendments and impacts, serious adverse events (SAEs) and compensation, informed consent and audio-video recording, monitoring and auditing of research, and future working of ECs.

Results: Seventy-nine percent of ECs are of the opinion that the new regulations/guidelines will add to their existing burden in the process of review and approval, providing subject protection and research oversight. Even though 68% of ECs stated that they are comfortable with SAE assessment and compensation determination, they state that there is variability in calculation of compensation amount using the formulae. An overwhelming majority (80%) of ECs stated that they were not in favor of centralized EC for providing review, approval, and oversight of clinical studies.

Discussion: Ethics Committees act as local regulator for clinical trials at sites providing Human Subject protection. The survey captures the contemporary issues faced by the ECs and also raises important questions on the ease of doing research, oversight of approved research, and administrative burden on the EC.

Conclusion: Recent changes in regulations have on the one hand empowered Ethics committees but brought in challenges in the way that they provide oversight and monitor research carried out at the site.

Keywords: Amendments, Central Drugs Standard Control Organization, ethics committees, regulations

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INTRODUCTION

Institutional and Independent Ethics Committees (ECs) have as their primary mission the protection of human research subjects.[1] In India, ethics review of the proposal occurs in parallel to the regulatory review. As per the Indian regulations, all ECs must be registered with the Central Drugs Standard Control Organization (CDSCO) to approve and authorize clinical trials.

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There are more than 1051 ECs (with 64 new ECs registered in 2016 alone) which has been registered with the CDSCO as of October 31, 2016.[2] The majority of these are the Institutional ECs. The registration has been issued for 3 years, after which the The Regulatory agency in India – Drug Controller General of India (DCGI) under the CDSCO – has over the course of

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2013–2016 introduced several amendments to the regulations overseeing the conduct of Research in India.[3,4] Several of these changes/new requirements affect the functioning of the EC, for example, need for mandatory registration with CDSCO, determining the appropriateness of Investigator to conduct studies (number, complexity, and site capabilities), and assessing and determining quantum of compensation.[3-7]

The Ethics Council of Indian Society for Clinical Research (ISCR) conducted a questionnaire survey among EC members to understand the effect of the changes in regulations/amendments on the EC's day-to-day functioning. This paper evaluates the responses received as part of the survey and raises questions on the ease of doing research, oversight of approved research, administrative burdens, and logistical difficulties from the perspective of ECs.

METHODOLOGY

A survey questionnaire was designed by the Ethics Council of ISCR covering both operational and functional domains of ethical review process. The questionnaire had a total of 25 questions divided into five domains.

The domains included (i) awareness about recent changes/amendments to regulations and how it impacts the EC, (ii) serious adverse events (SAEs) and compensation, (iii) informed consent and audio-video (AV) recording of informed consent process, (iv) monitoring and auditing of research approved by the EC, and (v) future working of ECs.

The questions were framed keeping in context that some of the ECs may be reviewing only academic research. The questionnaire used both Likert scale responses to assess level of agreement or disagreement with the statements and also open-ended questions. The respondents to the questionnaire also had opportunity to provide free text wherever a question with Likert scale was deemed inappropriate/inadequate to capture the information/comments. If a respondent had different roles in different ECs, only the first response was captured. In case of questions for which there were no responses, it was not analyzed as there was no opportunity to query the respondent due to the anonymous nature of the survey.

A total of 100 ECs were identified based on the registration details maintained by the CDSCO on their portal.[2] It was decided to do both an online and a face–to-face survey. The online survey was sent to EC's E-mail IDs available with the Ethics Council of ISCR. The face–to-face survey was attempted when there was a meeting (public) wherein EC members participated. To account for different and conflicting responses from the same ECs, it was decided to have only one member from a named EC to complete the survey and this was deemed to be the one who was approached/available first. Likert-type items fall into the ordinal measurement scale, and descriptive statistics was used to represent the data.

RESULTS

Even though a pan-India survey was rolled out, responses were obtained from a total of 25 registered ECs across mainly the western and southern parts of India. Overall, the respondents provided answers to all questions in the survey.

The majority of respondents were Member Secretary as their stated role in the EC [Figure 1].

In the regulations section [Table 1], lack of clarity with requirements for renewal of registration and cumbersome documentation (29% each) were identified by respondents as the most critical challenge(s) encountered by EC in the renewal of EC registration with the regulatory authorities (DCGI). Other reasons that were identified included lack of institutional support (17%), lack of response/acknowledgment of the submitted documents from DCGI (13%), and resource constraints at the institution to support EC (8%).

ECs shared that the recent changes in the regulations governing clinical research were a significant improvement over previous regulations. ECs noted that changes are too many, too often, and were a burden to the EC. ECs felt that the training needs of the EC members are high and that there is a lack of clarity on role and function of independent EC.

Serious adverse event and compensation

Majority of the ECs [Table 2] were of the opinion that they are able to navigate the process and timelines for SAE and Compensation. ECs also shared that compensation

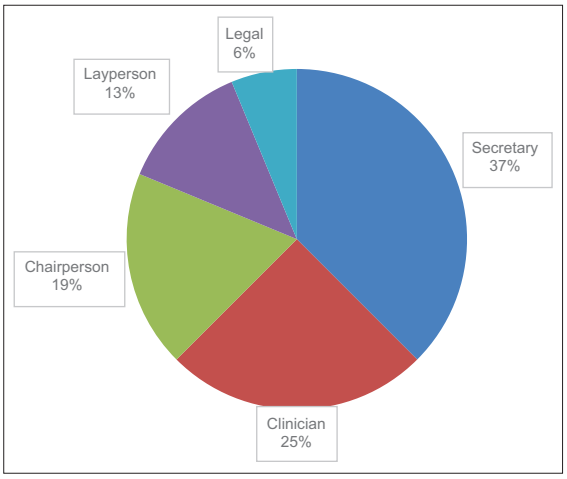

Figure 1: Role distribution of ethics committee members participating in survey

determination should be outside the ambit of institutional EC; there is a need for clarity on compensation for academic research; training on compensation is also needed for EC members; defining "risk" in the compensation formula is challenging; dataset that comes for EC review of the SAEs is inadequate and that EC members would welcome additional training in determining compensation for clinical trial injury.

Informed consent and audio-video recording of informed consent process

ECs stated [Table 3] that the investigators in their institutions have no issues with AV recording of Informed consent but the ECs do not review the same for ongoing studies.

Monitoring and auditing

Sixty percent of ECs [Table 4] have no experience of being audited (by a third party) or inspected by regulatory authority. ECs also stated that it is difficult to motivate members to conduct audits of ongoing studies. Some ECs stated that audits must be done mandatorily and that it requires workforce, time, and training.

Future perspectives

Fifty-six percent of ECs [Table 5] responded that they have a plan to implement electronic (paperless) submission of documents for review.

Table 1: Regualtions

Statement	Strongly agree (*n*%)	Agree (*n*%)	Disagree (*n*%)	Strongly disagree (*n*%)
Do you think that the recent circulars brought out by DCGI in the 1st week of August 2016 which makes the EC responsible to take decisions (number of trials per investigator, hospital bed provision for the institution conducting clinical trials, etc.) will increase the burden on the EC inappropriately?	29	50	13	8
As an IEC/IRB member, do you feel empowered to take a decision on approving the number of studies that an investigator conducts?	5	59	32	4
Your IEC/IRB has a training plan and members are trained when new regulations are rolled out	32 (29)	44 (54)	24 (17)	0

DCGI=Drug Controller General of India, EC=Ethics Committee, IEC/IRB=Institutional Ethics Committee/Institutional Review Board

Table 2: SAE and compensation

Statement	Strongly agree (*n*%)	Agree (*n*%)	Disagree (*n*%)	Strongly disagree (*n*%)
The current regulations on SAE and compensation are appropriate and adequate with respect to what has to be reported, to whom, how and provide the timelines for the same	12	56	32	0
Your IEC/IRB has encountered no issues in deciding the compensation to be paid to the subject (based on the revised compensation guideline and the calculation formula therein)	12	48	28	12

IEC/IRB=Institutional Ethics Committee/Institutional Review Board, SAE=Serious adverse event

Table 3: Informed consent and audio video recording of informed consent process

Statement	Strongly agree (*n*%)	Agree (*n*%)	Disagree (*n*%)	Strongly disagree (*n*%)
The informed consent process currently implemented at our institute is adequate	24	52	24	0
For an ongoing study, our IEC/IRB reviews AV recordings, in cases of, reports of noncompliance/protocol deviations, in the informed consent process	8	36	52	4

IEC/IRB=Institutional Ethics Committee/ Institutional Review Board, AV=Audio-video

Table 4: Monitoring and auditing

Statement	Strongly agree (*n*%)	Agree (*n*%)	Disagree (*n*%)	Strongly disagree (*n*%)
Your IEC/IRB has a well-devised plan/SOP to visit the sites for monitoring during the study conduct	8	28	60	4
Your IEC/IRB has visited sites for monitoring ongoing studies	16	20	36	28

IEC/IRB=Institutional Ethics Committee/Institutional Review Board, SOP=Standard operating procedure

Table 5: Future perspectives

Statement	Strongly agree (*n*%)	Agree (*n*%)	Disagree (*n*%)	Strongly disagree (*n*%)
Do you believe that there should be two committees - one reviewing the ethics part and another committee reviewing the scientific part of the research in each institute?	24	40	24	12
Do you think that one common central EC should be tasked with reviewing a multicenter study in India instead of multiple IEC/IRB	4	16	48	32
All IEC/IRB should be accredited, by a recognized body to improve the quality and working standards	24	56	16	4

IEC/IRB=Institutional Ethics Committee/Institutional Review Board, EC=Ethics Committee

DISCUSSION

The authors received only 25% responses to the survey which was sent to ECs across India, mostly the southern and western region. The number of ECs registered in the southern and western region together account for 77% of total registered ECs[4] and the distribution of trial sites are also higher in this region when compared to the North and Eastern states (data from Clinical Trail Registry of India).[8] The sample could be seen as representative of the "voice" of the more active ECs in the country. As the response size was small, it was decided to interpret the results descriptively as well as provide percentages where appropriate rather than give percentages for every response as it may give rise to bias for the reader. The three major concerns of the EC for the renewal of registration with CDSCO were cumbersomeness of the renewal process (28%), lack of clarity on required documentation for renewal (28%), and lack of Institutional support (16%). The CDSCO portal where the ECs are registered shows that there are at least 64 ECs which have been accorded registration in 2016. It is not clear from a sponsor (academic/industry) perspective as to how many of the existing ECs which were registered in 2014–2016 have had their registration renewed.

The new regulations or changes to existing regulations are posted on the DCGI website as General Statutory Rules (GSR) or administrative notices. Unless the ECs are frequently checking for updates on the DCGI website, it is easy to miss them. Lack of awareness and understanding of recent regulations and GSRs released by the government can lead to inconsistencies in EC review and approval at the site. It also paves way for audit and inspection findings in those studies which were done as multicenter studies. Most importantly, this can lead to delays in regulatory approval if the study was intended to support marketing authorization.

The majority of ECs had a training plan when new regulations/amendments are released. The overwhelmingly positive response could be due to the fact that the ECs surveyed belonged predominantly to tertiary level institutions in tier 1 and 2 cities which have larger share of both academic and industry sponsored studies. There are 1041 ECs which are currently registered with CDSCO. Independence and competence are hallmarks of a well-trained EC. The training and education of EC should focus on encouraging the EC to attain these benchmarks.[9] Currently, there is no way for sponsors to check whether there is any training documentation. An online accredited portal which provides standardized training on current and changed regulations will be required as the regulatory agency continues its streamlining process and more changes are expected in the future. An online training portal will also ensure that new members of ECs will have a standardized and relevant training that they can undertake rather than take recourse to material which is available on general public domain. A certification process will also ensure that this system is robust in ensuring appropriate training of ECs, conducted in a timely manner and also documented.

Serious adverse events and compensation

Majority of the ECs are familiar with the process and method to calculate the compensation amount based on the revised regulations enacted in 2013.[3] Ensuring uniformity and fairness in compensation payments in a trial is a challenge faced by the ECs. Even though the formulae provide standardization, there are variables like the assessment of "risk factor" for a trial which can lead to variability in arriving at the final compensation amount. Since different ECs in India are at different stages of evolution and maturity (with some having good processes, expertise, and experience while others have no experience), can also can bring in additional level of variability.[10]

AV recording of informed consent came into existence[5] since 2013, but there is still a debate on whether it is helping in better subject understanding about research or whether it is another administrative burden without empowering subject. A Cochrane review[11] published in 2012 for assessing the effects of audio-visual information interventions regarding informed consent compared with standard information or placebo audio-visual interventions regarding informed consent for potential clinical trial participants concluded that the value remained largely unclear, although trends are emerging with regard to improvements in knowledge and satisfaction. In India, where AV recording of informed consent is a mandatory regulatory requirement for clinical trial conduct (revised in 2015 and deemed to be required only in clinical trials conducted with an NCE/NBE in vulnerable populations),[12] it is important to carry out operational research to determine its value in terms of improving subject understanding, satisfaction, willingness to participate, and decrease anxiety or other psychological distress. An operational research of this nature should be conducted by an impartial stakeholder to inform governmental policy decisions for the betterment of clinical research in India.

There have been discussions at several forums as to whether India needs a centralized EC for review and approval of multicenter studies (academic/industry sponsored) or if local review is sufficient. The advantages of centralized ethics review include a single application form, standardized requirements and assessment, no variations in time-to-respond, access to expert panels, and greater consistency of reviews.[13,14] The advantages of institutional ECs (local) review process are as follows: EC members are more familiar with the investigator, the research settings, monitoring of ongoing research is easier, and it is possible to impose institutional sanctions for violations by investigators. One major disadvantage that ECs stated was that a central EC can become bureaucratic and lose the ability to respond to requirements of all stakeholders

quickly. This can become a bottleneck for approval of projects whether academic or industry.

Accreditation of ECs and investigator sites was proposed to be conducted under the auspices of the Quality Council of India (under the National Accreditation Board of Hospitals) as announced in 2014,[15] but there is no further clarity on the path forward. A small number of ECs (20%) are accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP)[16] and/or the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER).[17] In India, many ECs do not have the institutional backing or funding or resources to go through a rigorous accreditation process such as the AAHRPP or the SIDCER. The vast majority of the academic and private institutions work with bare minimum staff for their administrative requirements. As the DCGI and the government have taken steps to unshackle clinical research in Institutions by delinking academic nonregulatory research from their purview, the EC members surveyed clearly believe that this will increase the workload of already burdened ECs further. As sites start to conduct more research in the coming years a mechanism/process should be evolved where a third party accreditation body can plan, conduct, assess, and accredit the large number of institutions which have never been accredited by either international or national body. This will build further confidence among all stakeholders in the research conducted at sites.

ECs predominantly from the Southern and Western region responded to the survey, and thus, the results and the discussion of the survey cannot be generalized. The survey used Likert scales predominantly for collecting responses as they are quick, easily quantifiable, and subjective to computation of some mathematical analysis. Likert scale unfortunately is unidimensional and only gives options of choice, and the space between each choice cannot possibly be equidistant.[18] The authors would like to acknowledge the limitation of the Likert scales used in this survey.

CONCLUSIONS

Clinical research in India is undergoing a slow rebirth along with concurrent regulatory reforms. ECs have been performing the task of local regulator for clinical trials which are being conducted at sites ensuring ethics and data quality, thereby providing Human Subject protection and adherence to Good Clinical Practice. Many of the changes in regulations have further empowered the ECs in discharging their duties in the institution but have also brought in challenges in several critical areas e.g. assessment of causality and compensation for SAEs, determine site and Investigator capabilities to conduct the study etc. Institutional support, ongoing training of EC members on amendments/new regulations that govern research, monitoring, and continued oversight of the research conducted at the institution will be keys to ensuring confidence in subject safety protection and data quality.

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Conflicts of interest

There are no conflicts of interest.

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