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Abstract

A study to assess completeness of project application forms submitted to Institutional Ethics Committees (IEC) of a tertiary care hospital

Objectives: To review Ethics Committee (EC) application forms and to find out similarities and differences in content of five ECs forms in India. **Materials and Methods:** The completeness of EC application forms was assessed on the following themes: title, study team, sponsor responsibility, scientific aspects, patient safety, regulatory permissions, Informed consent process from 2008-2009. Application forms (available online) of 5 ECs were studied and compared. **Results:** A total of 445 application forms were analyzed, 382 were academic, 63 were sponsored. The common deficiencies in academic studies were inappropriate titles (25.13%), lack of budget details (90%). More than 95% studies had not mentioned the method of recruitment. The issue of vulnerability was not marked in more than 50% of studies. Compensation for participation/injury was poorly stated in academic (99%) studies. Among industry sponsored studies, 98% were compliant with regulatory permissions and 41% were CTRI registered. The information pertaining to Informed Consent was mentioned in all forms. Comparative analysis of application forms of 5 ECs showed that the requirements for submission were similar except 1-2 ECs asked for additional information like percentage of time allotted by investigator for studies, GCP training of study team, certification by investigator regarding accuracy of local versions of Informed consent. **Conclusion:** Our study recommends that increased awareness and vigilance by investigators of academic studies regarding submission of applications to EC will increase efficiency and speed of review process. A common application form for all ECs across India would be an important step to achieve uniformity in functioning of ethics committees.

Key words: Academic, application form, clinical trial, completeness, ethics committee, sponsored

INTRODUCTION

One of the essential documents required to be submitted along with the research proposal to the Ethics Committee

is an 'Application Form'. A well designed and duly filled application form provides the snapshot of the entire study which helps not only the Ethics committee (EC) members in the review process but also the administrative staff to maintain study related records. World Health Organization Special Programme for Research and Training in Tropical Diseases (WHO TDR), Indian Council of medical Research (ICMR) and Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use (ENTR/CT2) guidelines state that EC is responsible for establishing

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well-defined requirements for submitting an application for review of a biomedical research project.^[1-3] Majority of the Ethics Committees in India have their own format of application form which is formulated based on their standard operating procedures (SOPs) and requirements stated in the ICMR guidelines 2006. An EC application form should ideally have elements which capture important aspects of protocol and informed consent documents and also provide checklist of other documents to be submitted for EC review.

The process of review may seem cumbersome and time consuming if application forms are not adequate in their content or investigators do not comply with requirements of submission. Deficiencies on the part of investigators with respect to filling of application forms increase the work of EC as clarifications are often asked from investigators for missing information.^[4,5] On the other hand, some researchers have commented that institutional and independent ECs differ in their requirements of application procedures which often lead to difficulties in obtaining ethics approval for multicentre studies.^[4-6]

In view of the above, the idea to review application forms submitted to the Institutional ECs was conceived. Further, it was felt that application forms of different ECs available online could be studied to find out the type of information asked by various ECs from investigators at the time of project submission. Hence the present study was planned with the objectives to review completeness of EC application forms received by the institutional ECs and to compare format of application forms of 5 different ECs in India.

MATERIALS AND METHODS

This was a retrospective observational study which was initiated after obtaining Institutional Ethics Committee (IEC) permission. The application forms of research projects submitted to the two Ethics Committees, Ethics Committee for Research on Human Subjects (ECRHS) and Committee for Academic Research Ethics (CARE) of the institution during 1st January 2009 to 31st December 2009 were analyzed for completeness. Further, a comparison was made among format of application forms of five ECs in India whose forms were available online.

The application forms submitted to the two IECs were assessed with respect to the following themes: Number and type of studies submitted, completeness of the application forms with respect to: title, study team, sponsorship and sponsor responsibility, sample size, method of recruitment, compensation to study

participants, regulatory permissions, information related to informed consent process, other information related to declaration of conflict of interest, plans for storage and maintenance of data, signatures of principal investigator, co-investigators and heads of departments, etc. We did not review protocol or informed consent documents and other study related documents which were submitted with the application form.

The EC application forms of five different ECs in India were analyzed to find out the similarities and differences in the project application forms.

RESULTS

A total of 445 application forms of research projects submitted to the two IECs of the institution from 1st January 2009- 31st December 2009 were analyzed. There were 382 academic and 63 sponsored studies. Out of 382 academic studies, 271 (71%) were dissertations and 111 (29%) were investigator initiated. Out of 63 sponsored studies, 48 (76%) were sponsored by pharmaceutical industry and 15 (24%) were sponsored by government agencies [Figure 1].

Majority of academic and government sponsored studies were of epidemiological type. Among the industry sponsored studies, majority were phase III drug trials. The other common types of studies were basic sciences related, nutritional products and procedure related techniques [Table 1].

Observations Related to Contents of the Application Forms: The following findings were noted on reviewing contents of the application forms:

Title, study team, Sponsorship and sponsor responsibility [Table 2]

In 25% of academic studies, there were short forms used in titles. In studies which involved inter-departmental collaborations, the list of investigators mentioned in the form was incomplete. Details of collaborating parties were missing in 27/32 (84%) of academic studies. Majority of academic studies (90%) did not state information regarding amount and source of funding and sponsor of the study.

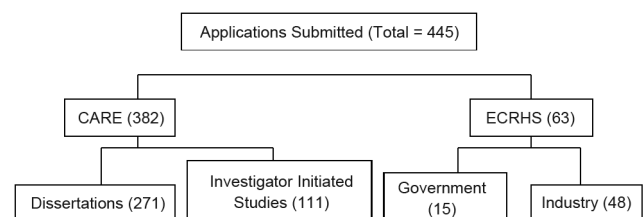


Figure 1: Number of studies submitted to the two institutional ECs

Table 1: Types of studies submitted for review

| Type of study | Academic studies | Government sponsored | Industry sponsored |
|--|------------------------------|--------------------------|----------------------|
| Epidemiological | 40.84% | 46.67% | 6.25% |
| Phase I clinical trial | 10.47% | 6.67% | 2.08% |
| Phase II clinical trial | | Nil | 14.58% |
| Phase III clinical trial | | Nil | 43.75% |
| Phase IV clinical trial | | 6.67% | 14.58% |
| <i>In vitro</i> study | Nil | 6.67% | 2.08% |
| Basic sciences related | Nil | 26.67% | 10.45% |
| Others | 0.52% (Yoga) 0.79% (Cadaver) | 6.67%- Ayurvedic studies | 36.25%- Food Product |
| Procedure/ technique related study | 38.48% | Nil | Nil |
| No. of studies involving collaboration | 8.38% | 86.67% | 22.92% |
| Device study | 8.9% | Nil | Nil |

Table 2: Discrepancies observed in the application Forms

| Points in application form | Academic studies | Government sponsored | Industry sponsored |
|---|------------------|----------------------|--------------------|
| Title: Use of short forms | 25.13% | 6.67% | 2.08% |
| Incomplete list of investigators | 9.42% | 13.33% | 0% |
| No indication of collaborating investigators/ institute | 84.38% | 23.08% | 27.27% |
| Missing sponsor information/ Budget amount | 90.16% | 20.34% | 4.16% |

Table 3: Discrepancies in research methodology related information

| Points in application form | Academic studies | Government sponsored | Industry sponsored |
|--|------------------|----------------------|--------------------|
| Sample size not mentioned | 10.21% | 2.08% | 0% |
| Type of study stated incorrectly | 16.23% | 60% | 14.58% |
| Vulnerability not specified | 47.91% | 53.33% | 68.75% |
| Method of recruitment not stated | 95.81% | 93.33% | 91.67% |
| Use of biological fluids not mentioned | 15.97% | 13.33% | 39.58% |

Research methodology related information [Table 3]

The number of participants to be recruited was not mentioned in 10% of the application forms of academic studies. In 60% of government studies, the study design was not specified for most of the studies and for some of these studies, the type of study was not matching with the title. The information on whether the study population to be recruited was vulnerable was not specified. The method of recruitment was poorly addressed in majority of the application forms in all the three categories. Fifteen percent of academic, 13% of government funded and 40% of the industry funded studies did not provide any information regarding use of biological materials (such as blood samples).

Compensation to participants [Table 4]

Statements about compensation for participation were not mentioned in 99% of academic studies. Further, amount of compensation for participation was not stated in majority of academic and government sponsored studies. Provision related to compensation for study related injury was not written in 99% of academic studies and 93% of government sponsored studies.

Regulatory permissions [Table 5]

The compliance of investigators of Government and industry-sponsored studies was good with respect to obtaining the signatures of investigators or co-investigators or heads of the department/institute. Missing signatures were observed in 9% of academic studies. Majority of the industry and academic studies had filled the information related to regulatory permission except for 7% of government studies.

Table 4: Information submitted related to compensation to participants

| Points in application form | Academic studies | Government sponsored | Industry sponsored |
|--|------------------|----------------------|--------------------|
| Statement related to Compensation for participation: missing | 98.95% | 60% | 33.33% |
| Amount of compensation for participation: missing | 66.67% | 66.67% | 37.50% |
| Statement related to compensation for injury: missing | 98.95% | 93.33% | 16.67% |

Table 5: Information about regulatory permissions

| Points in application form | Academic studies | Government sponsored | Industry sponsored |
|---|------------------|----------------------|--------------------|
| Missing signatures of investigators/co-investigators / head of department | 9.42% | 0% | 2.08% |
| No mention about permissions from DCGI/ HMSC/ Institute Head | 1.31% | 6.67% | 0% |

Informed consent process

The statements pertaining to informed consent, the risks/benefit assessment and privacy and confidentiality were mentioned in all the application forms in the industry sponsored, Government as well as academic studies.

Other observations

In 41% of the sponsored studies, the information related to registration of clinical trials in Clinical Trials Registry

of India (CTRI) was written. This aspect was not marked in the application forms by investigators of government and academic projects. Regarding declaration of conflict of interest, investigators of industry studies seemed to be more vigilant as 81% of the studies had statement about 'no conflict of interest' whereas only about 7% of government studies included such a statement. In 84% of industry studies, the duration of data storage and maintenance (ranging from two years to 15 years) was stated. None of the academic studies mentioned about it. Sixty three percent of the industry sponsored studies mentioned about existence of data monitoring committee and 37% of industry sponsored studies mentioned about the provision for interim analysis of data.

To meet the second objective of the study, analysis of the application forms of 5 ECs located in different zones of India: 4 institutional and 1 non-institutional was done. The noteworthy findings are presented below:

- The points seeking information related to study protocol, informed consent process and also about submission of various documents were included in application forms of all the 5 ECs.
- One EC either required submission of summary of the study protocol in 500 words. Another EC needed key points of protocol which were required to be filled in the application form itself.
- Three application forms contained spaces to be ticked or crossed against responses such as yes/ no and not applicable for different aspects related to protocol or Informed Consent Document and for submission of various study related documents.
- Number of ongoing studies being done by each principal investigator and co-investigator was required by 1 EC.
- One EC specifically asked for percentage of time that principal investigator will devote for each ongoing project
- Information on status of the test drug whether marketed and if marketed submission of package insert of the drug was required by 3 ECs.
- For drug interventional studies, documentation regarding GCP training of team of investigators was needed by 3 ECs.
- Curriculum vitae of all team members: investigators and study coordinators was required by 3 ECs.
- Submission of manufacturing license for herbal drugs by the State FDA was required by 1 EC.
- One institutional EC needed certification by PI ensuring accuracy of translation of local language versions of the Informed Consent Document.
- In case of collaboration with Indian or foreign laboratory/clinic/ institution, administrative sanction from the Director/ head of the Institution was mandated by 1 institutional EC.

- The non-institutional EC asked for site profile – details about facilities and equipments and 'no objection certificate' for review from Dean/ Medical Superintendent of the trial site.

DISCUSSION

Research involving human subjects has increased in the developing world, including India.^[7] The expanding field of clinical research is placing a huge responsibility on ECs. The process of review of a research study by an EC can be divided into two integrated components: procedural issues such as checking of application form for completeness, checking consent and other study related documents and proper review of the study proposal by the EC members.^[8,9] Lack of compliance by investigators to complete procedural formalities may delay the timelines of EC review process. The procedural issues generally lead to increase in the burden of work and may cause rift between researchers and ECs.^[10]

A review of literature showed that there were no studies which reviewed EC application forms and assessed compliance of investigators with respect to filling of application forms in India. This paper describes common deficiencies which we found in the application forms submitted to our institutional ECs and the comparative findings of the applications forms of five different ECs in India.

The discrepancies in titles, missing statements related to vulnerability of study population, conflict of interest, registration of clinical trials, provision of compensation for participation and compensation for study related injury were found in majority of academic studies. Most of the academic studies were investigator initiated studies done by junior faculty or by residents for dissertation. It is possible that these junior investigators filled the forms improperly. Beginners in research may not be adequately trained in GCP or research methodology so as to understand relevance of submitting information on these aspects to the EC. Ignorance on the part of investigator could be another possible reason. Imparting training to investigators and creating awareness will help to streamline the correspondence between EC and investigator; saving valuable amount of time spent on review process. The ICMR guidelines require that source of funding and fund allocation for the proposed research study should be reviewed by EC.^[2] The details about budget and budget amount were stated in less than 10% of academic studies. Many of these academic studies are self-funded and investigators may feel it is irrelevant to mention about funding when no external sponsor is involved. Such practices should be discouraged. The points related to data

monitoring committee, plans for interim analysis of data and data storage were not marked in the application forms of the academic studies. These aspects are probably not relevant to most academic studies. Since the application form is generic for an EC, it is suggested that an option of marking 'not applicable' needs to be provided for some of the elements of application forms.

Registering clinical trials is considered an ethical and moral imperative. The launch of the CTRI provides opportunities to all in India to fulfill this imperative. The CTRI requires that registration of drug trials should be done before recruitment of first patient in the study and it is mandated by DCGI. For clinical trials initiated after 15th June 2009,^[11] Registration in the CTRI is still not compulsory for observational studies. This is well reflected in our finding that sponsored studies have 41% registration whereas government and academic studies are not registered.^[12]

The positive findings were contents related to Informed Consent process, the risks/ benefits assessment and privacy and confidentiality statements were duly filled in the applications forms indicating the awareness of local researchers about importance of informed consent process in conduct of research.

The review of application forms of 5 ECs revealed that the forms were designed as per national and international guidelines and showed considerable similarities in their contents.^[1,2] This was in contrast to the findings of the study conducted by Ezzat *et al.* which found that each of 16 research ethics boards of different institutions had a varied application forms and nine of them had two or three step application process.^[13]

It is a good practice on the part of one EC to ask for number of ongoing studies done by investigators and also take assurance of time commitment from principal investigator. In many medical institutes, senior faculty members take up number of research projects as principal investigators at one time. Although there is a hierarchy of unit members to carry out study related activities, it is important that the principal investigator takes up the overall responsibility and devotes adequate time for each study. An EC cannot put a cap on number of studies a researcher can undertake at one time, however, it can question investigators regarding his/her commitment in terms of time and duties. Such time allocation can be calculated based on the draft guidelines.^[14] Submission of curriculum vitae and GCP training certificates of investigators is necessary to ensure adequacy of qualifications and experience of investigators undertaking research. This is in accordance with principle of professional competence stated in the ICMR guidelines.^[2]

The requirement by one EC about certification by principal investigator ensuring accuracy of translations of Consent Documents seems appropriate for academic studies as a step to ensure that participants will understand the study and then provide consent. Although, it is ideal to ask for back-translations including certification regarding authenticity of translation from an authorized translating agency. This issue is especially applicable to Indian settings since India is a multi-linguistic nation.

We found that non-institutional EC asked for site profile and 'no objection certificate' from Dean/ Medical Superintendent of the trial site for review of study by non-institutional EC. Since non-institutional ECs review studies submitted by investigators from distant places, they should make sure that investigators have adequate facilities, infrastructure in addition to expertise to carry out proposed research. The concurrence of the administrative head of the site is always desirable as it ensures accountability and transparency in research.

A limitation of our study is that only 5 application forms of different ECs were considered for comparison. Our observation that the requirements mentioned in application forms were similar cannot be generalized unless data from a large number of ECs in India is studied.

A detailed application form requiring investigators to fill in relevant details about all the essential elements of protocol and the informed consent document is desirable. Such application form may become lengthy but it will be very useful to EC members to identify important ethical issues; especially while reviewing studies with complex study methodology. It would be most ideal to have a uniform application form for all ECs in India which can be made available online by the national governing authority.

CONCLUSION

Our study recommends that increased vigilance by investigators of academic studies regarding submission of applications to Ethics Committees will increase efficiency and speed of review process by EC. Regular audit to help identify problems related to content of the application form and periodic revisions to make the form investigator friendly will be useful. A common application form for all ECs across India would be an important step to achieve uniformity in functioning of ethics committees.

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