**An Audit of Institutional Ethics Committee Queries Raised after Initial Project Submission at a tertiary referral center.**

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**Abstract:**

An Institutional Ethics Committee (IEC) ensures the rights and safety of the research participants by reviewing research protocols. There is no definitive measure on how much the review process translates into safe-guarding the participants’ rights and safety. Therefore, we proposed to assess the extent to which the queries are perceived by the investigators to have an impact. Query letters and the replies over a two-year period were evaluated. The outcome measures were the domains of queries and the agreement/disagreement between two investigators’ perspective (one affiliated and another unaffiliated author) on the impact of the query to the study. Thirteen studies (Investigator initiated studies [IIS]: 7 and Pharmaceuticals sponsored studies [PSS]: 6) were included. The total number of queries were 364 (IIS:n=106; PSS:n=258;p<0.001). These included administrative [126(34.62%)], ethics-related, [138(37.91%)] and scientific 100(27.47%) queries/comments. The overall agreement between the two investigators was 12.9% (p<0.001) showing that perspectives between investigators are grossly different.

**Keywords:**

Audit; Institutional Ethics Committee; Perspectives; Queries; Comments

**Introduction:**

An Institutional Ethics Committee (IEC) is a body that although affiliated with the institution, functions independently of it.[1] The main goal of an IEC is to safeguard the rights, safety and dignity of the research participants under its purview. One of the main responsibilities of an IEC is the risk-benefit analysis of each research proposal.[2] This is ensured by the IEC by reviewing research protocols submitted to them for the scientific merit and ethical considerations before the project can be initiated.[3] They also monitor ongoing trials to ensure compliance to the approved protocol.[3]

The New Drugs and Clinical Trials [NDCT] rules 2019 has made it mandatory that IECs are registered with the Central Licensing Authority (CLA)[1] Some IECs also get themselves accredited with accreditation agencies such as the National Accreditation Board for Hospitals and Healthcare Providers (NABH), Strategic Initiative for Developing Capacity in Ethical Review (SIDCER), Association for the Accreditation of Human Research Protection Programs (AAHRPP) and likewise.[2] The registration and accreditation processes ensure that the systems and processes are in place but do not necessarily provide assurance of the quality and adequacy of the review process following project submission. This study was envisaged with an objective that an audit of the queries raised by the IEC during the initial review of a research proposal involving human participants would shed light on the quality of review performed by the IEC.

**Methods:**

*Ethics and study design*

Being an audit, the study was exempted from review by the IEC (EC/ OA-121/2019) [3]. Our institution has three IECs (IEC– 1 for regulatory studies and IEC– 2 and IEC– 3 for academic and other biomedical research). After initial review, the IEC secretariat conveys its comments and queries. These are received in a structured format under the following heads- general queries, protocol queries, informed consent document queries, indemnity insurance policy document queries, clinical trial agreement queries, case record format queries and miscellaneous queries.

**Sampling frame and eligibility criteria:**

Queries raised by the IEC to research proposals submitted for initial review from the Department of Clinical Pharmacology affiliated to a tertiary care referral hospital, constituted the subject matter of the study. Inclusions were all studies [whether pharmaceutical industry- sponsored studies (PSS) or investigator- initiated studies (IIS) and whether interventional or otherwise) submitted to the IEC during a two-year period from July 2017– June 2019. Studies that were exempt from review by the IEC such as meta- analyses, audits, non-biomedical studies and research on data available in public domain were excluded.

**Objectives:**

The primary objective was to determine the number of queries and comments that were related to the various domains; administrative, scientific or ethics- related [see below for definitions][4] and to assess the different types [not relevant at this stage of submission, already available in the initial submission but was missed by IEC, IEC requested for a simple paraphrasing of text, Not present in the initial submission submitted by the investigator, IEC required further clarification for better understanding and clarity] of comments/ queries. These assessments were based on consensus among all the study investigators.

The secondary objectives were to assess the extent to which the queries/ comments were perceived to improve the science, safe-guard the rights and safety of research participants or have an impact on the quality of the conduct of the study and to assess for differences between the investigator- initiated studies (IIS) and pharmaceutical industry-sponsored studies (PSS) with regards to the primary objective.

**Classification of queries and comments into various domains:[4]**

1. *Administrative:* These included queries and comments on clinical trial agreement, indemnity insurance policy, other site IEC approvals and administrative and regulatory approvals.
2. *Scientific:* These included queries and comments related to methodological aspects of the study (e.g. related to appropriateness of study design, comparator, eligibility criteria of participants, study site and outcome measures, sample size estimation and statistical methods.
3. *Ethics-related*: These included queries and comments related to participant safety and well-being, participant rights, maintenance of confidentiality, participant remuneration, research related injury, risk-mitigation aspects and informed consent process.

**Study procedures:**

All the study investigators independently classified the queries into domains and types. In case of discrepancy, a decision was taken based on consensus. Two other investigators [NJG – author affiliated to the department (AAD) investigator and SBB – author unaffiliated to the department (AUD)] independently assessed for the relevance of the query under the following options namely (1) Unlikely, (2) Neutral and (3) Likely. In case of scientific or ethics related queries, relevance was assessed by answering the question, how likely is that specific query going to improve the science of the study or safe guard the rights and safety of participants respectively, in the perspective of the evaluator. In case of administrative queries, the relevance was assessed by answering the question, how likely is the query going to impact the quality of the conduct of the study in the perspective of the evaluator.

**Outcome measures:**

The primary outcome measures were the number of queries under various domains and types. The secondary outcomes measures were the agreement/ disagreement between the AID’s and AUD’s perspectives and the differences with regards to the primary outcome measures between IIS and PSS.

**Data Management and Statistical Analysis Plan:**

Data entry was done using Microsoft Excel (Publisher: Microsoft Corporation, Redmond, Washington, USA, 2016) and Statistical Package for Social Sciences (SPSS) for windows, version 20.0 (Publisher: IBM, Armonk, New York, USA, 2011) was used for data analysis. Descriptive statistics and inferential statistics were used. Demographic data, the domains and the types of queries were summarized using frequency and percentages. Comparisons between IIS and PSS studies were done using chi-squared test and post-hoc Beasley’s technique with Bonferroni’s correction for discrete data or Mann-Whitney U test for continuous data. Cohen’s kappa was used to assess for agreement between AID and AUD’s perspective. Statistical significance was set at p < 0.05.

**Results:**

**Demographics:**

The Department of Clinical Pharmacology submitted 19 research projects to the IEC for review. Six studies were exempt from review and hence were excluded from further analysis. Of the 13 eligible studies 6/13 (46.2%) were PSS and the rest [7/13 (53.8%)] were IIS. The total number of queries/comments in the selected studies were 364 with 258 (70.9%) of them from PSS and 106 (29.1%) from IIS. The median (Interquartile range) of queries per study in the PSS and IIS was 43.00 (29.25, 55.25) and 15.00 (11.00, 19.00) respectively and this difference was statistically significant (p < 0.001). All the PSS were regulatory studies and none of the IIS were regulatory in nature.

**Analysis of domains:**

Of the 364 queries, 126 (34.62%) were of administrative domain, 138(37.91%) were ethics-related and 100 (27.47%) were of scientific domain. There was a significant difference in the number of comments per domain between IIS and PSS (Pearson’s χ2 = 35.331; p = 0.000000021275) the details of which along with the results of the post-hoc analysis is tabulated in Table-1. The ethics related queries (p=0.0007) were significantly more in the PSS whereas scientific queries (p <0.0001) were more in the IIS.

**Types:**

With regards to the types of queries, 42 (11.54%) were not relevant at that stage of submission; 51 (14.01%) were pertaining to information already available (submitted at the time of initial submission) but IEC had missed; 67 (18.41%) IEC requested paraphrasing; 154 (42.31%) not submitted in the initial submission but missed by the investigator; 50 (13.74%) were relevant with need for further clarification. There was a significant difference in the number of various types of queries between IIS and PSS (Pearson’s χ2 = 56.001; p < 0.00000001), the details of which, along with the post-hoc analysis are tabulated in table-2. Queries that were not relevant (p=0.0030) and those due to IEC missing information (p=0.0003) were higher in PSS while queries due to investigator missing to provide information to the IEC during initial submission (p<0.0001) were higher in IIS.

**Investigators’ perspectives:**

The AUD evaluated 221 out of 364 (60.71%) queries to be unlikely to have any relevance whereas the AID classified 85 out of 364 (23.35%) in the same category. Favourable and neutral stands were taken for 129 (35.44%) and 19 (5.22%) queries/comments by the AID whereas the AUD classified 145 (39.84%) and 134 (36.81) queries/comments as favourable and neutral respectively. The details of domain wise perspective evaluation and the Cohen’s kappa are depicted in table-3. The overall agreement was 0.129 (p<0.001).

**Discussion:**

This audit was conducted in a tertiary care referral centre to ascertain the domains of the comments/queries raised by the IEC and how many of these comments / queries actually translate to safe guard the rights and safety of research participants. We report that there were significantly greater numbers of queries in the PSS when compared to the IIS. Scientific queries were more in the IIS whereas ethics related queries were more in the PSS. The overall agreement about the nature of queries, between the AID and AUD was significantly low (0.029, p<0.001).

The quality assurance process of the IECs in the USA is very well established through frequent inspections conducted by the United States Food and Drug Administration (USFDA) since 1980.[5] In India, although the registration of IECs with the, the Central Drugs Standard Control Organization (CDSCO), has been mandated since 2013, inspections from the CLA are not very common, especially given the scenario that more than 1000 IECs have registered with CDSCO.[6] In general, the purpose of auditing IECs is to appraise their members on how their functioning translates into an assurance that the ethical review of research proposals is carried out as per the established standards, thereby protecting the rights and safety of the research participants.[7] Thus, the authors believed that this audit would provide our IECs with an opportunity to identify short-comings and improve their functioning that translates into better participant protection and safety.

The mean number of queries in the PSS were significantly more when compared to the IIS and comparatively, there were more ethics-related queries and not much of scientific queries in the PSS. This is probably because, the PSS are usually prepared for regulatory submissions and are often approved by the CLA and/or other sites’ IECs at the point of our IEC submission. Further, there are dedicated and experienced protocol development teams in the industry that oversee protocol development and writing. Therefore, the IEC do not find errors in science. However, the IECs are vested with the responsibility to review for specific local issues that are unique to the site and are predominantly ethics-related,[7] thus explaining the reason for more ethics related queries in PSS as seen in our study. This is also the reason for a greater number of queries in the PSS as protocols are prepared in a generalized way that suits most centres and not covering all local site-specific issues. Secondly, PSS have more complex issues like post-trial access, arrangements of compensations, transport of biological samples outside the institution and/or outside the country, status of regulatory approvals *etc.*[8] which is usually not the case in IIS. On the other hand, IIS are largely single- centre studies and they do not usually undergo regulatory review. So, there is much more flexibility in incorporating the suggestions from the IEC and modify the science of the protocol.

We found that many queries in PSS were related to information/ documents that had already been submitted to the IEC. This is probably because most PSS submissions are voluminous as they are usually regulatory in nature. Another possible reason could be the lack of dedicated full-time staff at most IECs in India, [9] who review these proposals thereby potentially missing out already available information. Many a times, IEC staff are contractual with higher attrition rates who may not be vested in the review process. On the contrary IIS submissions had more queries related to mandatory information that were not available in the initial submission. One possible reason could be that the IEC dossiers of IIS submissions are mostly prepared by young researchers or post graduate students (in case of a thesis) unlike PSS submissions which are usually prepared by dedicated professionals who work in teams. New researchers or students who get admitted in academic institutions like ours usually do not undergo a formal training on the pre-requisites of an IEC submission and they usually learn “on the job”. Another reason could be that, research often takes a back seat to clinical practice in hospital like ours and there is no dedicated research secretariat.

An audit conducted at our institution previously had reported that there was a total of N=1387 studies during the time period January 2011 to August 2014 of which 818 (59%) were dissertations of postgraduate students and 406 (29%) were IIS contributing to the major bulk of the proposals being reviewed by IEC.[10] Thus, if formal trainings are conducted periodically, a lot of effort and time may be saved by both the researchers and the IEC as the number of queries pertaining to mandatory information/documents to be submitted would drastically fall. The IEC could also provide templates for protocols for different types of studies and for consent and assent forms at its website for the guidance of young researchers. In addition, better supervision of the dissertation protocols by guides may also help in minimizing the queries raised by the IEC. This would, in turn, decrease the resource crunch faced by the IECs and would also comparatively increase the efficiency of their working with the available manpower.

With regards to the two investigator’s perspectives on the relevance of the queries, we report that there was more of a disagreement rather than agreement. Both investigators perceived that many ethics-related queries would have had a positive impact. However, the science and administrative queries saw a major difference in opinions. Although a lot of it could be attributed to the differences in their role played as a stakeholder in clinical research, as they influence one’s perceptions and their differential training (One Investigator was a clinical pharmacologist and the other a paediatrician).[11] This finding indeed validates the need for the presence of IEC members from various backgrounds – both scientific and non-scientific and the importance of quorum and consensus-based decisions.

The strength of our study was that the perspectives of in-house investigator and an independent investigator were compared. Our study has a few limitations. It was an audit of IECs within one institution which follow the same SOPs. Thus, findings form this study may not reflect the status of other IECs in the country. Secondly, the time period chosen was of two-years that corresponds to just one term of the IEC members. There may be differences in the findings with change in members from time to time. Also, the three senior investigators of this study were members of IECs either within or outside the institution which was a potential conflict of interest.

**Conclusion:**

The IECs exercise extreme caution, whenever feasible, to try and safeguard the rights and well-being of the research participants as is noted by the greater number of ethics-related queries seen in the PSS. They also strive to perfect the science of the protocol as is seen by the greater number of scientific queries in the IIS. The authors believe that the appointment of full-time staff in IECs would go a long way in improving the quality of review by avoiding unnecessary queries that increase the time of initial approval. Furthermore, formal training of young academic investigators or those newly employed within the institution on IEC dossier preparation specific to the IEC of the institute, will minimise investigator side errors in submitting all mandatory documents thereby saving time and resources. An investigator vested in the study has a totally different perspective from the others as observed in our study. Thus, we recommend that the composition of IECs be as diverse as possible such that the different opinions from each member of the IEC would ultimately strengthen the project in all facets.

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**Conflicts of Interest:** None to declare

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**Tables – 1: Proportion of queries in different domains of IIS and PSS**

|  |  |  |  |
| --- | --- | --- | --- |
| **Domain** | **Pharmaceutical industry sponsored**  n= 258 | **Investigator- Initiated**  n=106 | **p value\*** |
| **Administrative (%)** | 98 (38.0) | 28 (26.4) | 0.0350 |
| **Scientific (%)** | 48 (18.6) | 52 (49.1) | 0.0007† |
| **Ethics-related (%)** | 112 (43.4) | 26 (24.5) | <0.00001† |

\* Adjusted level of significance after Bonferroni’s correction; p = 0.008

†: Significant

Figures in parentheses indicate percentages

**Table-2: Proportion of queries of different types in IIS and PSS**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Pharmaceutical industry sponsored**  n=258 | **Investigator Initiated**  n=106 | **p value\*** |
| **Not relevant at this stage of submission** | 38 (14.7) | 4 (3.8) | 0.003† |
| **Already available in the initial submission but was missed by IEC** | 47 (18.2) | 4 (3.8) | 0.0003† |
| **IEC requested for a simple paraphrasing of text** | 56 (21.7) | 11 (10.4) | 0.0113 |
| **Not present in the initial submission submitted by the investigator** | 78 (30.2) | 76 (71.7) | <0.0001† |
| **IEC required further clarification for better understanding and clarity** | 39 (15.1) | 11 (3.4) | 0.2328 |

\*Adjusted level of significance after Bonferroni’s correction; p = 0.005

†: Significant

Figures in parentheses indicate percentages.

**Table-3: Investigators’ perspectives on queries’ impact on the study conduct**

|  |  |  |  |
| --- | --- | --- | --- |
| **Domain**  Cohen’s Kappa  (p value) | **Perceived impact** | **AIDs perspective**  n (%) | **AUD’s perspective**  n (%) |
| **Administrative**  κ = 0.079  (p = 0.095) | Likely | 33 (26.19) | 39 (31.20) |
| Neutral | 53 (50.00) | 3 (2.40) |
| Unlikely | 40 (23.81) | 89 (71.20) |
| **Total** | **126 (100)** | **125 (100) \*** |
| **Scientific**  κ = 0.027  (p = 0.422) | Likely | 23 (23) | 10 (10) |
| Neutral | 53 (53) | 4 (4) |
| Unlikely | 24 (24) | 86 (86) |
| **Total** | **100 (100)** | **100 (100)** |
| **Ethics-related**  κ = 0.104  (p = 0.080) | Likely | 89 (64.49) | 80 (57.97) |
| Neutral | 28 (20.29) | 12 (8.70) |
| Unlikely | 21 (15.22) | 46 (33.33) |
| **Total** | **138 (100)** | **138 (100)** |

AID – Author affiliated to the department; AUD – Author unaffiliated to the departmentf

\* Did not wish to answer for 1 query