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Background

Research is essential for advancement of knowledge and science. Medical research that involves humans, including those that involve identifiable human data or material must be conducted in accordance with the ethical principles laid down in the declaration of Helsinki [1]. Adherence to these principles helps to protect the rights and wellbeing and ensures respect of study participants.

Research proposals involving human subjects must be reviewed and approved by an Ethics Review Committee (ERC) prior to commencement of research. The assessment by an ERC is needed in order to ensure respect and autonomy of the research participants and to ensure beneficence, non-maleficence and justice [1]. Owing to the biological similarities seen between man and animals, animal research has been an integral aspect of research. Prior data from animal studies are almost always needed before a new product can be tried out in humans. Animal research should also be conducted in a manner that minimizes the impact on animals involved [2,3]. Thus, the ERCs' main functions include evaluating research projects based on their scientific relevance, technical and operational feasibility and reviewing ethics of the proposed research.

Over the last few years there has been an increase in bio-medical research projects being conducted in Sri Lanka. This is largely due to the government initiative to promote research. Most of these are investigator initiated while a few are industry sponsored multi-centre phase 2 or 3 clinical trials. Phase 1 industry sponsored clinical trials for new chemical entities are not allowed in Sri Lanka at present.

In the absence of national guidelines on ethics review and the ERCs in Sri Lanka rely on international guidelines such as the Declaration of Helsinki [1] and CIOMS [4] when reviewing protocols. While providing a sound basis for ethical review, these lack guidance on social and cultural issues specific to the country and the ERCs have to rely on the collective expertise and judgment of its members to reach a consensus on such issues.

Although there is a national framework for the conduct of clinical trials, Sri Lanka lacks laws to govern the conduct of research and ethics review committees (ERCs). There is no local mechanism to evaluate or accredit ERCs resulting in inequalities in the quality of ethics review provided by different ERCs where some committees are perceived as being "more rigorous" and "strict" than others. In the absence of a national mechanism for accredit ERCs, many are now seeking recognition by the Forum for Ethics Review Committees in the Asia and the Western Pacific (FERCAP) under its Strategic Initiative for the Development of Capacity in Ethical research (SIDCER) [5]. In the absence of a legal framework, ERC remains a major form of research oversight.

22/ **Identifying reasons for delays in ethics approval: Experience of an institutional ethics review committee**

- Chandanie Amila Wanigatunge, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka
Email: caw@sjp.ac.lk, (Corresponding author)
- Shamini Prathapan, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka
- Gizelle Malinka Warnacula, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka
- Rochelle Shanika Tanner, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka

Abstract

Ethics review is a mandatory process in research involving humans and animals. Incorrect applications results in resubmissions leading to delays in obtaining ethics approval. This study was conducted to ascertain reasons for resubmission of protocols to an ethics review committee. A randomly selected sample of proposals submitted during a 3 year period for an institutional ethics review committee were analyzed to find the reasons for resubmission. The qualitative variables were analyzed through the calculation of absolute and relative frequencies

Two hundred and sixty nine protocols were submitted during the study period of 3 years. Protocols for observational studies accounted for 89% while clinical trials and animal studies accounted for 7.8% and 3.3% respectively. The majority (86%) of principal investigators were those with a medical degree. Average stop clock time was 23.4 days. Majority (67.3%) were reviewed over 2 meetings to reach a final decision. Of the 95 reasons for returning the protocols to researchers, protocol related issues (66.3%) and informed consent form issues (29.5%) were the major reasons. The main protocol related issues were those in methodology (41%), statistical issues (54%) and inadequate risk benefit analysis (14%). Clinical trial related protocols needed more reviews before approval was granted.

Delays in reviewing due to ERC were minimal. Most of the protocols that required resubmission had issues pertaining to methodology and informed consent forms or processes. These are easily corrected and can be avoided with careful attention to ethical issues by researchers when preparing the protocols.

The ERC of Faculty of Medical Sciences (FMS), University of Sri Jayewardenepura (USJ) is an institutional ERC established in 1995 to facilitate research of its academic community. ERC FMS USJ was granted recognition by the FERCAP under its SIDCER recognition programme and is one of the 8 ERCs recognised by the Ministry of Health of Sri Lanka to approve phase 2 and 3 clinical trial protocols.

ERC FMS USJ performs full board reviews of about 70-90 protocols a year and entertains applications from any researcher who wish to conduct research involving human participants in Sri Lanka and those involving animals. In addition to the duly completed appropriate application form, a detailed study protocol, a letter of approval issued by the relevant higher degrees board for protocols submitted for higher degrees, data collection tools, information sheets, consent forms and translations of all relevant documents are required at the time of submission.

Review by ERCs is considered by many researchers as an obstacle for research [6]. Review time and hence time for approval if prolonged may result a study site being taken off a multi-centre study and ERC reviews are therefore considered as undue delays by some researchers [7].

Sometimes proposals are reviewed over several meetings and this delays the final decision. The delays in review could be due to increasing workloads of ERCs over time, complexity of research protocols that might need external expert evaluations or even poorly prepared submissions submitted by Principal Investigators (PIs) which would lead to multiple resubmissions. Lack of knowledge about research participant protection among researchers is another factor. Understanding the issues that lead to an ERC delay due to resubmissions would help applicants to prepare their application better. In audits of ERCs in Brazil and Spain the main reasons for resubmission of protocols were issues in the informed consent form and methodological and statistical issues [8,9].

Identifying the reasons for resubmissions would help to identify what corrective measures need to be taken to minimize delays in decision making of ERC. This would in turn, will help researchers to better prepare their applications. We therefore performed an audit on a sample of applications submitted to ERC FMS,USJ from 2012 – 2014 to ascertain causes of leading to resubmission of protocols.

Method

The study was conducted between April – August 2015. Using a skip interval of three, every third protocol in the database was selected to achieve the required sample size of 88 to be analysed to find the reasons for resubmission.

All documents pertaining to individual protocols are kept in separate protocol folders in the ERC office and these were used for data extraction. Investigator profile was determined from the application forms and the other data pertaining to each protocol were extracted from the relevant minutes and the correspondences in the protocol folders. Data was entered into an Excel

worksheet. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS, version 15). The qualitative variables were analyzed through the calculation of absolute and relative frequencies. This project was approved by the ERC FMS USJ (ERC55/14).

Stop-clock time – i.e. time taken for principal investigator (PI) to respond to ERCs queries – was calculated separately to help determine its contribution to the time needed for final ERC approval.

Results

A total of 269 protocols had been submitted for review for the period January 2012 – December 2014. The majority (n=239, 89%) were for observational studies while applications for clinical trials and animal studies accounted for only 21 (7.8%) and 9 (3.3%) respectively. The majority (n=203, 76%) were self-funded. Eighty eight (32.7%) protocols were approved without requiring further clarifications. The average time taken by the ERC to reach a final decision (inclusive of stop clock time of 23.4 days) was 58 days. The mean number of meetings needed by ERC for the final decision to be reached was 1.8 meetings with a mode of 2.

Eighty-eight protocols were selected at random for further analysis. Of these, 93% (n=82) were human studies while animal studies and audits accounted for 5.7% and 1.1% respectively.

Of the human studies observational studies were the commonest study type (n=78, 89%) while 8% (n=7) were interventional studies / clinical trials. Studies related to herbs and other traditional medicinal products accounted for 3.4% (n=3). Sixty five (74%) of the protocols were submitted by Principal Investigators (PIs) with a basic medical degree. Of the 88 selected protocols 47 (53.4%) had required resubmission. All clinical trial protocols required resubmission and were approved after an average of 2.4 meetings. When the stop clock time was excluded the average time taken for approval was 55.3 days which is nearly equal to 1.8 meetings

The main reasons for returning the protocols to PIs for resubmission are given in table 1.

Table 1: Reasons for returning the protocols to PI for resubmission

Reasons	Total (n=95)	
	N	%
Issues in protocol	63	66.3
ICFs	28	29.5
Administrative issues	4	4.2

* Total is > 47 as some protocols had more than 1 reason that needed to be addressed.

There were a total of 95 reasons for returning the protocols to PIs for resubmission. The reasons were categorized under 3 main domains – protocol, informed consent and administrative. Of the protocols requiring resubmission, the majority (57%) were due to

issues pertaining to a single domain (e.g. protocol or informed consent process) while 43% had issues related to multiple domains. Every clinical trial protocol had issues related to multiple domains that needed to be corrected or clarified. The main reasons for returning protocols were those related to the methodology of the study (46%) and issues in the informed consent forms (27%). The issues related to protocol and informed consent forms/process are given in tables 2 and 3 respectively.

Table 2: Issues related to protocol leading to resubmission (n=47)

Issues In protocol	N	%
Clarifications in the study instruments and its translations	12	25.5
Lack of or inadequate risk benefit analysis	11	23.4
Lack of detail in the methodology	9	19.1
Failure to mention or doubts regarding issues related to sample size	6	12.8
Clarifications in recognition and provision of treatment for adverse effects and side effects	5	10.6
Inadequate definition of Inclusion criteria	4	8.5
Inadequate definition of exclusion criteria	4	8.5
Clarifications in title	4	8.5
Fate of samples	3	6.4
Inadequate justification/literature review	2	4.3
Inadequate definition of the general and specific objectives	1	2.1
Poor definition of terms used in the protocol	1	2.1
Failure to mention or doubts regarding study setting	1	2.1
Total no of methodological issues	63	

In nearly one fourth of protocols returned to PIs, the information sheets contained inadequate information. Administrative issues were very few in numbers, accounting to only 8.5% of the total issues.

Issues in the protocols in clinical trials and in non-clinical trials were compared. On average, clinical trials took longer to receive approval and most (n=5/7) had needed 2.4 meetings for approval to be granted. Issues pertaining to study methodology, informed consent forms and translations and inadequate risk: benefit analysis were the leading causes requiring resubmission for clinical trial related protocols. These were similar to those seen with non clinical trial applications. The issues pertaining to risk: benefit analysis in clinical trial applications are given in table 4.

Table 3: Issues related to Informed Consent leading to resubmission of protocols (n=47)

	N	%
Inadequate information provided in information sheets	11	23.4
Language too technical	6	12.8
Translations not provided or inconsistency in translations	6	12.8
Contact details of PI not mentioned	5	10.6
Total no of issues related to informed consent	28	

Table 4: Issues related to Risk Benefit Analysis in clinical trial protocols (n=7)

	N	%
Inadequate information on treatment of adverse effects	4	57.1
Failure to provide Biological Material Transfer Agreement	2	28.6
Failure to provide or inadequate risk benefit analysis	2	28.6
Lack of information on likely adverse effects	1	14.3
No justification for use of the drug on a vulnerable population	1	14.3
Lack of appropriate medical personnel on the team	1	14.3
Role of sponsor with regard to ownership of data collected not clarified	1	14.3
Insufficient details on risk to participants	1	14.3
Failure to mention fate of the samples once study is completed	1	14.3
Total number of issues related to risk: benefit analysis in clinical trial protocols	14	

The non-clinical trial protocols had more reasons for resubmissions. These were related to methodology, inadequate literature reviews, definition of the objectives and justification of the study setting.

Discussion

Delays in obtaining ethics approval can be due to delays in processing by the ERC and/or due to incomplete submissions by the investigators to the ERC. The reasons need to be identified to enable corrective measures to be taken and thereby minimize delays in approval process. To the best of our knowledge this is the first study to analyse experiences of an institutional ethics review committee in Sri Lanka.

The results of our study indicate that approximately two thirds of the applications to the ERC during the study period contained scientific, ethical or administrative defects which necessitated resubmission. This is comparable with that of a similar study done in Spain [9] but nearly twice that of a study in Brazil [8] where 68% had been reviewed in a single meeting. Methodological issues were the main reasons for protocols needing resubmission in our study. Among the ethical issues, inadequacies in the

informed consent process was the commonest cause that required resubmissions.

Informed consent is the cornerstone of research ethics. Adequate information presented in a manner easily understandable would help the participants to make an educated decision on taking part in the research. It is also important for researchers, especially those who are also in clinical practice, to recognise that there are differences between informed consent for participation in research and informed consent in patient care [10]. The main issues associated with informed consent forms (ICFs) in this study were inadequate information provided, language too technical to understand the contents and inaccuracies of translations in to Sinhala or Tamil. The main problem noted in the translations was the use of written language which is in most instances not in common use, a problem encountered when profession translators are involved. The issues seen with ICFs in this study were similar to those in other similar studies [11]. Researchers must be aware that the ICF is meant for the potential participants [10] and the language and contents should therefore be appropriate for their level of education and understanding. It is the responsibility of the researcher to ensure that the ICF is appropriate in both contents and the language used. In addition to the procedures that will be carried out during the study, the ICFs must contain information regarding background, justification and objectives of the study. The responsibility of the ERC is to ensure that the ICF is written in a manner that the research participant understands the research, especially the potential risks and benefits thus enabling him to make an informed decision [11].

In the absence of a separate and independent scientific review, it falls on the ERC to review the scientific aspects of the protocol as scientifically invalid research is unethical in that it exposes research subjects to risks without possible benefit [4]. Scientific review must consider the study design, including the provisions for avoiding or minimizing risk and for monitoring safety [4]. In our study, the protocol related issues (53.8%) that necessitated resubmission were mainly those related to study instruments and its translations (25.5%), methodology (19.1%), sample size calculations (12.8%) and risk benefit analysis (14.1%). These were seen in both clinical trial and other research protocols submitted to our ERC. However, information on management of adverse effects/events (57.1%) were seen more with clinical trial protocols while issues related to study instruments and their translations were more in other types of protocols.

An awareness of what may lead to delays in ERC approval would help researchers to plan their submission better. This includes paying attention to the protocol especially the methodology, to the informed consent process and preparing the information sheets and consent forms appropriately and other necessary documentation. Investigators should be aware that scientific and operational aspects of the study must be understood not only by review experts in that field of

research, but also by reviewers from other research fields, and even reviewers who are not linked to the research but are members of the community [11]. Most of these can be easily corrected if attention is paid while preparing the protocol and necessary documentation [11]. Familiarity of ethical considerations by researchers is helpful when discussing the issues raised by the ERC and negotiating these with it [12].

The delays can also occur with the review process itself by the ERC. This could be due to the workload of ERC members who in nearly all instances would be providing an honorary service in addition to their usual work. Non-availability of the required expertise necessitating the project being sent to external reviewers is another potential cause for delay. ERCs should have mechanisms to minimize delays while providing a good quality and timely review. ERC FMS, USJ has a policy of resending the documents to the original primary reviewers if they are resubmitted for major modifications and a process of Chairperson's approval for minor modifications to reduce delays associated with the administrative process.

The average time taken by ERC, FMS USJ to grant approval for a project from the time of its submission was 2 meetings (57.9 days) inclusive of the average stop clock time of 23.4 days which is the time taken by the investigators to respond to ERC comments. In most instances a single resubmission addressing the issues of ERC was all that was needed for approval. The approval time was longer for clinical trial protocols which took an average of 3 meetings to reach a decision. Investigators of such trials would also take longer (average of 34.6 days) to respond to ERC's queries. This would necessitate the protocol to remain in the agenda for extra meetings without it being taken up for discussion. The ERC approval time can be further shortened if the investigators take note of the scientific and ethical issues when preparing their protocols.

Conclusions

Ethical analysis of a research project must be viewed as a fundamental and essential step by all those involved in conducting research involving both humans and animals. Researchers need to have greater awareness of the rights of individuals who participate in biomedical research, especially with regard to protecting the autonomy of participants and ensuring their safety and wellbeing. Greater understanding of research ethics by those conducting research would help to minimize delays associated with the ethics review process. The interactions between the researchers and ERC should be viewed positively by all involved to ensure that the research is conducted in a scientific and ethical manner.

Competing interests - CAW was Chairperson, SP was Secretary and RT and GW were administrative assistants of ERC, FMS USJ during the study period.

Authors' contributions - CAW proposed the initial conceptual framework for the research and were

responsible for overall conduct of the project. CAW, SP and RT and GW were involved in the protocol design, writing and editing the manuscript. CAW, SP and GW contributed to collection and analysis of data including the statistical analysis. CAW prepared the first draft and SP wrote the second draft. All authors were involved in subsequent editing and agreed on the final version.

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Whitehead's concept of the past as objective immortality with special reference to Tanabe's idea of world religion

- Makoto Ozaki, Ph.D.
Emeritus Professor, Sanyo Gakuen University, Japan
Email: orig57eter@orion.ocn.ne.jp

The Kyoto School philosopher Hajime Tanabe proposes a new idea of world religion in which Christianity, Japanese Buddhism and Marxism are to be unified in a dialectical way as the self-developmental synthesis in history in anticipation of the second religious reformation. It would probably be tenable in comparison to Hegel's idea of history in which abstract and implicit potentiality gradually comes to actuality, superseding each specific stage, until the unity of the whole is completely realized. Whereas for Hegel the Divine Spirit is the immanent agency operative throughout the progressive history, it is the task of human endeavor for Tanabe to construct such a project as unprecedented. How is this feasible? It might be highly productive of the actualization of potentiality to employ the Whiteheadian process which is composed of the subjective becoming for the future ideal and the objective being as the real potential inherited from the past with the view of the advance of human ideas. This piece may be tempted in adventure to open a novel phase of the hidden potential truth up to the actual reality as the Aristotelian *entelecheia*, suggesting the Hegelian Absolute as the effect or end qua the actualized beginning, in the event.

The past as Objective Immortality

With regard to Aristotle's distinction of actuality and potentiality, A.N. Whitehead makes a further distinction between pure potentiality and real potentiality in relation to actuality. While pure potentiality refers to the Platonic eternal ideas or universal forms, real potentiality is on the status of the past being which is no longer subjectively active but still remains the stubborn fact or given datum functioning as the efficient causation for the succeeding subjective actuality of becoming. For Whitehead, the past is never ascribed to nothingness but is rather immanent in the present as the objective immortality. For him, the world is composed of actual entities or occasions in succession of time which have the double structure of subject and object or superject in such a way that when the subjective act of becoming in the present completes and terminates its activity, it is negatively converted and turned out into the object as being without its own subjective immediacy. In other words, the past lives in the present with the vectorial transference to the future, and hence is still actual and active in the form of memory and causality for