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Protocol and Researcher's Relationship with Institutional Review Board

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ABSTRACT

The document of ethical approval is an important official requirement for research involving human participants worldwide. It is the process whereby an investigator submits the full research proposal and related documents including detailed informed consent process to an independent Institutional Review Board (IRB) for scrutiny. The process of seeking review and approval is necessary to ensure adequate measure are in place to safeguard and protect research participants as entrenched in the principles of The Declaration of Helsinki and The Belmont Report. It is the responsibility of every clinical researcher to obtain ethical approval, therefore, their obligation to understand the process of review and establish relationship with local IRB in order to enhance smooth review and approval. This article, therefore, explains clinical research and distinguishes between research and clinical care, clarifies briefly what constitutes a study protocol and describes the researchers' relationship with IRB

Keywords: *Clinical research, clinical practice, ethical approval, institutional review board, study protocol*

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INTRODUCTION

The idea of writing a study proposal is often the starting point after conceptualizing the research idea and defining the gaps to be filled. This is probably one of the most difficult aspects of human research, in particular among graduates and young investigators in academics. Writing a research proposal involving human participants requires paying attention to the basics of ethical standards in accordance with The International Council on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines (Bhuiyan and Rege, 2001). Worldwide, any research involving human subjects is expected to be subjected to review and approval of a properly constituted Institutional Review Board (IRB) which would examine the details of the protocol in order to safe guide the right and safety of future potential participants (ICH-GCP, 1996).

The ICH-GCP is a "harmonized standard guideline that protects the rights, safety and wellbeing of human research participants, minimizes human exposure to investigational products, improves quality of data, speeds up marketing of new drugs and decreases the cost to sponsors and to the public" (ICH-GCP, 1996; Sherke and Rao, 2001; Vijayananthan and Nawawi, 2008). When research complies with this standard, the public is reassured that the rights, safety and well- being of persons who participated are protected, in accordance with the principles of the Helsinki Declaration, and that the data are considered valid [Bhuiyan and Rege, 2001, WMA, 2004).

To be ethically acceptable,a clinical study must be reviewed and approved by the IRB. The IRB determines whether the risk to potential participants of the proposed study is minimized and reasonable in relation to the relevance of the expected knowledge and outcomes (WMA, 2004). However, the process of writing an acceptable study protocol related to the existing IRB and meeting the requirement for obtaining approval could be a challenging task for many students and young researchers. The purpose of this article, therefore, is to briefly explain what constitute a study protocol, describe the relationship of investigator with IRB and highlight the expectations of the IRB.

CLINICAL RESEARCH VERSUS CLINICAL PRACTICE

Clinical research or clinical trials are often confused with clinical practice (that is medical care). If the physician is also a researcher, this subject can be particularly confusing. When the physician provides the medical care, he or she develops a care plan just for the individual patients. But in clinical research, the lead researcher and his/her co-investigators must follow a set plan called the "study protocol" such that everyone including the patients are placed under obligation follow it (Barlow, 1981).

According to the Department of Health and Human Services (DHHS) Definitions (45 CFR 46.102), clinical research is any "activity designed to test hypothesis, allow conclusions and thereby develop or contribute to generalizable knowledge (expressed in theories, principles and relationship statements)" (USDHHS, 2018). Clinical practice entails administration of intervention and related-activities designed solely to improve the well-being of individual patients or clients and has reasonable expectations of success, it is intended to provide the particular individuals with diagnosis, preventive treatment or therapy. The aim of clinical research is to develop useful knowledge about human health and disease and ways of preventing, diagnosing and treating disease. The goal is not to benefit participants (although there are sometimes benefits) but the society at large because a relatively larger number of people than research participants would obviously benefit from the outcome of the research. Some of the differences between clinical research and medical care, as described on the website of the U.S. Food and Drug Administration (2018) are listed in Table 1.

In clinical research, people are the means to develop the intended useful knowledge and these people are undoubtedly at risk of being exploited. Thus, one of the intentions of ethics is to safeguard and protect the research participants from the potential risk associated with research (WMA, 2001). Confidentiality is an vital part of clinical research which dictates that personal information can be viewed by only those authorized to access it. It also means that only individual patients and researchers are aware of the clinical trial participants' personal identity and all medical information (Giordano et al, 2007). The results of a study are therefore usually only presented trends or results without mention of specific participants data.

People participate in clinical research for different reasons (Alexander , 2010; Hussain-Gambles, 2004, Grady, 2005). Some people take part in research because of poor assurance of the available standard treatment options or some of the side effects cannot be tolerated. If standard treatment options failed, clinical trials provide another option for finding a new one. Some other people take part in trials because they want to help promote medical knowledge. Notwithstanding the reason for participation, the interest and safety of participants in research must always be protected. This is why there are existing government agencies, boards of institutional review, professional standards, informed consent and legal standards.

ROLES OF THE INSTITUTIONAL REVIEW BOARD

The Institutional Review Board (IRB) is a regulatory body constituted to protect the rights and well-being of individuals selected to participate in research exercises (CIOMS, 2002). The IRB must review all research involving human participants before it begins. In accordance with the regulatory authority and existing institutional policies, the IRB has the authority to approve, criticize and monitor all research activities within its competence and to require changes. A typical IRB should consist of at least five members with different expertise capable of providing comprehensive review of the research protocol and related documents, including the material transfer agreement.

The IRB also takes into account the proposed research's institutional, legal, scientific and social implications. Each IRB must have at least one member who is not an institution's employee or affiliate and one member who is not a scientist. The IRBs often work with several experts or consultants who play advisory roles and are asked to review the protocol on a regular basis, especially in their area of expertise. Research ethics committees (RECs) must be truly independent when drawing up a judgment on how best to protect the rights and well-being of participants in the trial. Their independence ensures that any potential conflict of interests is not a real conflict. RECs are therefore responsible for acting primarily in the interests of potential participants in research and the communities concerned. One of the principal duties of IRB is to ensure potential participants are given information about the trial which is complete and comprehensible. Without this information, potential participants cannot consent. In addition, there are limits to what a competent person can consent to and the REC is responsible for ensuring that the trial interventions are themselves lawful and reasonable.

THE STUDY PROTOCOL FOR IRB CONSIDERATION

The development of a clinical protocol is the beginning of every clinical investigation. The study protocol is a document that describes each stage of the study and answers relevant questions on topics such as: the problem of public health to be addressed, the questions to be answered, what objectives the study will achieve, how much power the study will have, and the impact of the findings on public health.

Table 1:
Clinical Research Versus Clinical Practice

	Clinical Research	Clinical Practice
What is the aim?	Answers specific questions through research involving numerous research volunteers.	Address the medical needs of individual patients.
Who Benefit?	Generally designed and intended to benefit future patients.	Intended to benefit the individual index patient.
How long?	Depends on the research protocol.	Requires real-time decisions.
Consent needed?	Requires written informed consent.	May or may not require informed consent.
Protections of subjects	Protected by regulatory agencies including IRB, professional organisations, and informed consent.	Guided by boards of medical practice, professional organisation, treatment protocols, and legal standards.
Access to Information	Considered confidential intellectual property.	Available to the general public through product labelling.

Adapted from the website of the U.S. Food and Drug Administration (2018)[9]

The most important document is perhaps the trial protocol (and any changes required during the study). The concern of IRB is often focused on whether the investigators' proposed study is scientifically sound and that the potential research participants would be adequately safeguarded and their right protected. A critical attention is also often paid to the potential risk the participants are likely to be exposed and the planned activities to mitigated them.

A well-setup IRB would look out for standard content of a protocol as stated in the ICH Good Clinical Practice guidelines, which includes the following topics:

1. Title Page, which include general information about the investigators and institutions involved in the study.
2. Background Information which gives the description of the problem to be solved and insight into rationale for the study. It also answers the questions on what is known and unknown about the problem intended to be addressed. This section of the protocol should also itemize the study hypotheses without ambiguity. It is the background section of the protocol that give indication of whether or not there is sufficient scientifically valid reason for the research. Otherwise the IRB reserves the right to decline approval.
3. Study aim and Objectives. The aim should address the overall objective of the study, while Specific Objectives should outline the measurable outcomes variables. These should not differ significantly from that in the approved proposal. Each of the objectives should be specific, measurable achievable within the scope and proposed setting(s) of the study.
4. Study Design. The choice of a suitable study design must be guided by the main research question intended to be answered. It encompasses type, duration, sampling and sample size determination. The IRB want the details of the justifications for the choice of the sampling method and the determination of the optimum number of required participants.
5. Selection and Exclusion of Participants. Research ethics committees examine eligibility criteria for studies to ensure that research does not take advantage of the vulnerable or exclude subjects who can benefit from study participation without good reason. Whether the benefits of participating in a study outweigh the potential risks is also a primary consideration in determining eligibility criteria. Ethical considerations can lead to the exclusion of pregnant and lactating women from children, adolescents and women in clinical trials. The exclusion of such patients does not, on the other hand, provide information on the benefits and risks of a drug in such patients, but may use the drug if approved. It is therefore important to consider whether these exclusions are really necessary on a case-by-case basis.
6. Treatment of Research Participants. Before giving approval, the IRB is responsible for ensuring that researchers clearly describe the details of treatments to be given to individuals participating in research. It is ethical only when all participants are offered the best standard treatments available. For this reason, the IRB frowns on the use of placebo, except when it can be absolutely proven that there is no other treatment option.
7. Data Management and Statistical Analysis. The essence of this section in the proposal to be submitted to the IRB is to highlight the steps that will be taken by investigators and sponsors in order to protect the fundamental rights and fundamental freedom of the natural person in accordance with the public interest in relation to the processing of personal data. It must be taken into account that no personal or sensitive data is collected that is not essential to the research. If possible, the necessary data should be collected without using personally identifiable information. If personal information is required, it is necessary to de-identify the data when it is collected or as soon as possible. In addition to the issue of the protection of personal data, the data analysis methods must follow a sound scientific approach capable of producing valid results. Analysis and reporting of all data are a laudable ideal, but it is not always possible to report everything that has been done, researchers must decide which data points and analytical methods be presented.
8. Ethical considerations. Most research ethics committee statutorily evaluate the extent of investigators compliance with the ethical principles as stated in the Declaration of Helsinki which details guideline governing the conduct of medical research (WMA, 2004). One of the main consideration is the detail of informed consent process. The Helsinki Declaration stipulated that "valid consent is properly informed and also freely given, without pressures such as coercion, threats or persuasion". The informed consent procedure must provide details on: (a) the purpose of the research; (b) eligibility criteria and why the individual is suitable for the research; (c) risks and benefits to potential participants; (d) the right to voluntarily accept to participate or refused to do so; (e) the right to withdraw from the study at any time without losing any of the entitled privileges; (f) evidence of consenting in the presence of at least an independent third party who is not part of the research; (g) how each participant will be given sufficient time to review the consent document and ask questions prior to consenting to participate; and (h) translation of the content of the informed consent to native languages for full understanding of the participants. It is also important to note that the consent document must have provision for the signature of all parties and contacts of the lead investigator and chairman of the IRB.

The Investigator and Institutional Review Board

The person responsible for conducting clinical research at the study site is an investigator. If a group of scientists conducts a study, the principal investigator is the team leader responsible for all activities (Sade and McKneally, 2002; Chilengi, 2009). On the other hand, the IRB is an official body experts constituted to protect the rights and well-being of research participants recruited to participate in research activities carried out under the supervision of an institution (Klitzman, 2012). An IRB reviews the appropriateness of the protocol, the

risks and benefits for study participants. It ensures that participants in clinical research are exposed to minimal risks in relation to any benefits that might result from the research (Kim, 2012). The responsibilities of investigators essentially focused on meeting the requirements for ethical review and approval in line with The International Council on Harmonisation (ICH) recommendations (ICH-GCP, 2001). Therefore, the lead investigators must demonstrate, in the protocol, that She/he:

a. Is properly qualified to assume responsibility for the conduct of the study;
b. Thoroughly familiar with the area of research interest and updated with the current knowledge;
c. Willing to comply with ICH-GCP guideline and other applicable regulations and be prepared for monitoring and audits; and
d. Responsible for ensuring adequate number of qualified staff and adequate facilities to complete the study.

In addition, the investigator is responsible for continuing communication with IRB even after approval has been given. For example, the investigator is expected to report adverse events or other incidents during research as well as protocol amendments. It is mandatory to obtain new written approval from the IRB before any subsequent changes to the protocol are implemented. Investigators are responsible for ensuring that a witness is present during the consent process if a participant or their representative is incapable of reading and a copy of the signed consent form is provided to each participant.

Difficulties of Investigators with Ethical Approval

The preparation of an application for ethical approval is no different from the writing of a grant proposal. Most local IRB simply expect as much detail as would be written in a typical research protocol in the application for review and approval but with sufficient details on how the investigator(s) would ensure safety and protection of research participants as enshrine in the ICH-GCP guideline. Investigations often encounter difficulty in fulfilling the requirements of the IRB because of their failure to pay close attention to details (Lincoln YS, Tierney WG, 2004). This lack of attention to details is often the cause of delays in receiving reviewers' comments and board's approval. Aside, there are many instances in which clinical researchers' view will conflict with their IRB's. If the researcher is not fully aware of the IRB expectations and the application process, a conflict may arise. Since the ethical review process can vary from institution to institution, the investigator needs to be aware of the application process in advance. Avoidable delays can also be eliminated by providing answers to all questions on the application form and explaining how investigator conduct research ethically and comply with all regulations as explicitly as possible.

One of the likely problems in the course of seeking proposal approval is that the review can take longer time than usual thereby limiting clinical researchers in some ways. The relationship between the clinical investigator and their patients often depends on trust, which is not easily in line with predictable timetables and deadlines. Furthermore, the collection of data ought to be carried out within the time frames determined by other important events or the convenience of participants. In view of this, investigators need to always start the application process early, perhaps, many months before data collection begins. It should also be noted that IRBs are often restricted by guidelines which have firm conditions for the establishment of a minimum member of reviewers that must be at their meeting and prevent review by e-mail exchange or proxy. In order to avoid delay in IRB approval, investigators should always consider when the faculty and staff who serve as reviewers for IRB are likely to be busy. However, with the emerging online method of submission of proposal in institutions across the world, it is likely that there would significant reduction in review and approval turnaround time. No doubt, the online systems would help to remove some paperwork and shorten the review process.

All human research must receive approval from IRB before the commencement of recruitment of study participants and the collection of data. The process of submission therefore potentially adds to the amount of work to be done in research process. Thus, a third area of potential problem is lack experience of working with IRB and the difficulty of coping with adding the demand of research to the burden of giving lectures and providing clinical service.

In addition, there may also be potential friction because voluntary reviewers for IRB may be unaccustomed with the area of focus of the study proposal and the underlying intentions of research by practitioners. The task of review is therefore a daunting task for such reviewers. For this reason, it is critical that the researcher explicitly describe the purpose of their study and the rationale. Addressing these issues can be particularly tricky for young and inexperience investigators. The ethical principles of beneficence require that researchers adopt the most appropriate design to maximize gains and diminish potential harm to participants.

Building Researcher Relationship With the IRB

In view of some of the possible hitches that may arise between researchers and IRBs, it is appropriate for researchers to undertake a deliberate study and familiarize themselves with the regulation for the submission, review and approval of research proposals in their institution. Investigators should visit IRB Web site and/or their office to seek for information. Investigators need to spend time to read any document on IRB 's application procedures and take note of planned training activities and instructions for submission. The investigators should determine whether their study meets the exempt or accelerated review criteria. The review of information published by IRB will help investigator to estimate the extent of the efforts required in preparing document for submission, including expected content of informed consent and procedures for handling individual participants' data.

It is also often helpful to ask another faculty for advice. Faculty members who have passed the process can help the researcher better understand the regulatory ethos of the institution. Another way that an investigator can facilitate an IRB 's prompt review and approval is to carefully prepare applications and additional documents according to the instructions. The main points to remember is the completion

of all application forms correctly and accurately. Investigator does not need to mention risks that are not likely to happen to avoid raising needless cause for concern. There is no need to state risks to participants that are unlikely to occur, thereby raising unnecessary red flag. It is important to distinguish clearly between confidentiality and anonymity, which the investigator promises to uphold. The researcher should also clearly state ethical guidelines for the protection of the privacy of participants.

Each researcher is a potential member of the IRB in his institution. Therefore, volunteering to participate in an IRB panel is a good practice. The participation of faculty wide research committees and other academic review panel is a common way of acquiring academic review experience in their institution. Volunteering as an IRB reviewer, however, offers an opportunity to investigators to learn the process of review and common errors in application for ethical approval. Lastly, every research needs training on biomedical ethics and responsible conduct of research.

Conclusion

The approval of a research proposal by the IRB is essential in order to carry out a study that meets critical global standard. It improves the impression that the results of any research involving human participants are valid and reliable. Seeking ethical review and approval from IRB does not have to be frustrating if investigators would take the advantages of accessing information on the process and work closely with the office staff of their local IRB effectively. For example, the application guideline can help to clarify issues.

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