Chapter 14
Protection of Subjects Participating in Clinical Trials

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Abstract Clinical trials constitute one of the final stages along the testing continuum that is so needed for the introduction of new products, methods, and groundbreaking technologies. Currently, most economies have recognized the importance clinical trials play as part of the entire value chain from idea to product. While most jurisdictions have developed systems of safeguards for the protection of human subjects involved in clinical trials, there are huge disconnects among jurisdictions, institutions and investigators. This article provides some generally accepted international standards and guidelines in relation to subject protection as it pertains to recruitment, confidentiality, monitoring, data storage and data transfer. The need for all trial protocols to be reviewed by a qualified and registered ethics committee, as well as that all legal requirements are met to ensure patient protection, is also highlighted. Since governments and industry see clinical trials as a critical and necessary step in the product development process, there is a need for more translational research, which will increase the demand for more participation in clinical trials. This article will therefore, also address the importance of patient protection if we are to meet these requirements.

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14.1 Introduction

Clinical trials constitute one of the final stages along the testing continuum that is so needed for the introduction of new products, methods, and groundbreaking technologies. These experiments using human volunteers are designed to determine whether the investigational product is safe and effective. The designs of clinical trials are typically conducted in stages where smaller safety studies involving healthy volunteers are initially planned, proceeded by larger scale studies involving numerous study subjects. Regardless of the phase of clinical trial, the governing health authority must grant approval of the study in addition to ethical approval by an expert committee before the trial can commence. These guidelines are in place in order to protect the safety and well being of the subjects participating in the clinical trial.

Adopted by the World Medical Association in June 1964, The Declaration of Helsinki outlined the concept of independent review of research protocols. The policy has been amended eight times since, most recently in October 2008 [1]. In 1997, the International Conference on Harmonization provided a guidance document on Good Clinical Practice (GCP) an international ethical and scientific quality standard for clinical trials [2]. This document is used by governments as guidance to regulate clinical trials involving humans. Compliance with GCP ensures the rights and safety of trial subjects are protected, consistent with the principles in the Declaration of Helsinki. In addition, there is also a general understanding that certain forms of risk are unacceptable to impose on human subjects. According to the Nuremberg Code, "No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur" [3, 4].

In 1979, the USA released a report titled the Belmont Report [5] to outline principles that should be followed for the protection of human subjects in research. This is the cornerstone document of the ethical principles and US regulations for the protection of research participants based on respect for persons, beneficence and justice. Currently, all federal departments and agencies supporting, conducting, or regulating research on humans have agreed to a set of ethical principles and regulations called the Common Rule. The Common Rule is in place to ensure that all of an institution's human research activities are guided by the ethical principles found in the Belmont Report. In Canada, the Tri-Council Policy Statement (TCPS) was first implemented in 1998 and has since been updated in 2010 to TCPS 2 [6]. This policy was formed with reference to leading international ethics policies, including The Declaration of Helsinki. With respect to India, clinical trials are governed by Schedule Y in the Drugs and Cosmetics Act [7], however; the competence of ethics committees in patient protection in clinical research has recently been questioned [8].

There is considerable variation in ethical and moral values between different countries and even disparities exist between different cultures within the same country. While ethics committees/institutional review boards as well as government regulatory bodies are official arbiters of ethical issues, the investigator should be well aware of any ethical issues that the design of the clinical trial may present.

This is particularly relevant when the protocol is for another country, social class or group, other than that of the person, who has developed the protocol [9]. Clinical trial investigators should be guided by ethical principles and patient protection should be a top priority [10]. This does not appear to be the case in some developing countries [11] including India [10, 12]. Quality of clinical trials depends not only on data integrity, but also on subject protection. With globalization, outsourcing and increasing complexities of clinical trials achieving global quality has become challenging [13].

Longstanding ethical principles require that risks clinical trial participants should be minimized and justified by the value of the data that the study is expected to produce [1, 2]. In a 2009 report by the European Parliament [14], the most common ethical violations in developing countries included: (i) clinical trial subjects were not adequately informed about the trial, the risks involved, and in some cases not being advised of their participation in a clinical trial at all; (ii) no guarantee to trial subjects of continuing treatment at the end of the trial; (iii) no local ethics approval of the protocol and (iv) experimental drug being tested against placebo rather than current approved intervention thus exposing patients to additional risks. Accordingly, this article describes some of the generally accepted international standards and guidelines in relation to subject protection in the conduct of clinical trials. We also describe the role of institutional ethics boards and the responsibility of the investigator through the design of the protocol. Attention is also paid to the importance of handling of data and personal information as well as the role of the monitoring process in ensuring patient protection during clinical trials. In addition, reference is also made to clinical trial registration and early termination of trials and how these aspects can contribute to protection of subjects participating in clinical trials.

14.2 Role of Institutional Review Boards in Protecting Subjects Against Unethical Practices

The ethics of clinical trials have been the subject of numerous publications and mandates that are used by institutional review boards on a daily basis. Institutional Review Boards (IRB) or Research Ethics Boards (REB) is a committee comprised of at least five members of various professional backgrounds who assemble to assess the research proposals for scientific content as well as to represent the best interest of the clinical trial participants. The committee is mandated by their institution to evaluate the proposed study for foreseeable risks and benefits, ethical implications and study design. Due to the nature of research as an investigation into the unknown, the likelihood of risk to the participant will be present. The type of risk that a human subject may be exposed to include: physical harm, psychological and/or social harm. Physical harm to a human subject include: injury from the use of equipment involved in the study, side-effect from the experimental treatments or allergic reactions [6]. When participating in a clinical trial a participant may

experience stress if the study involves answering questions that trigger recollection of unpleasant past events or even depression if they feel that the experimental treatment is not working. From a social point of view participants in the study should not be identified as participants as the illness or condition that they are suffering from may cause stigmatization in their community. The involvement in the study may also cause concern from loved ones if the health issues for the subject were not disclosed to those individuals.

It is the responsibility of the ethics committee to protect participants in clinical trials from unnecessary or avoidable risks by providing their expert assessment of whether the benefits of the clinical investigation out-weigh the risks and potential routes of eliminating or minimizing the risks that are present. The assessment of the clinical trial for ethical implications is another major aspect of the study that the ethics committee will assess. Potential issues such as an overwhelming presence of a power relationship between the study subject and the researcher, inadequate measures taken to protect the privacy and confidentiality of participants, cultural norms or practices that may affect the participant and the economic situation of the participant are some aspects that are assessed by the committee [6].

14.3 Protection of Subjects Through Clinical Trial Design

Pre-clinical data form the foundations for human studies. Before proceeding to early human testing, investigators and reviewers must determine whether the pre-clinical scientific foundation is adequate [4]. The design of the clinical trial also has an impact on the protection of the subjects. Recruitment and consent procedures, measures for protecting privacy and confidentiality, monitoring, data storage and transfer as well as appropriate use of patient sub-groups are elements for a clinical trial to ensure the well being of the clinical trial subject. Starting with the recruitment process the potential subjects must be provided with accurate, clear and concise information regarding their participation in the trial. Most often, recruitment material such as posters, bulletins, and radio or television advertisements must be approved by an ethics committee before they can be used for recruitment. In trials where rewards are offered, they must be offered to the prospective participants in a manner to minimize undue influence to participate in the trial. When introducing the clinical trial, the risk and benefits of participating in the research trial must be presented to persons interested in the trial as well as the inclusion and exclusion criteria for participation. The criteria for determining which patients will be included or excluded from the trial must be justified by the research question as there should not be a specific portion of the general population that is unfairly overrepresented or targeted for human trials and research. On the other hand, it is wrong to neglect or discriminate against individuals or segments of the population in order to gain a favorable outcome. All individuals should have an equal opportunity to participate in research. Groups such as children, the elderly, women, prisoners, ethno-cultural

minorities or those with mental health issues should not be discriminated against and should be treated fairly and equitably in the recruitment process. Measures such as having recruitment material available in another language or transportation to and from the trial site for the elderly should be considered and outlined by the researcher in the clinical trial design.

Once a potential participant shows interest in the clinical trial, additional information regarding the clinical trial is presented to the participant regarding the objective and goal of the trial, what is expected from the participant, procedures that they will undergo during the trial, the risks and benefits of participating, the handling of samples taken, handling of data acquired and alternatives to participating. Information is presented in lay language in order for the average person to fully comprehend the clinical trial. Potential subjects must be given sufficient time to ask questions and voice concerns before making an informed decision to participate. The decision of the individual to participate in the trial must be voluntary and free from coercion. A signed consent document must be attained by the researcher from the participant once they are in agreement to participate. In the event that the study participant is not in the right state of mind to give consent, an appointed guardian must also be involved in the consent process. In the event that the participant is under legal age, it is the responsibility of the parent or guardian to give consent for their child to participate in the clinical trial. This method of attaining consent is beneficial to the participant as they are presented with all aspects of the trial and where their decision to participate in a study is based on a thorough understanding of risks and benefits of participation. Therefore, the protection of human rights and the sanctity of informed consent are critical components of clinical research monitored by human subjects' investigation committees [15].

14.4 Handling of Personal Information and Data

Once the trial has begun and participants provide personal information, the researcher must have the duty to treat personal information respectfully and confidentially. Any personal information gathered must be stored securely and should not be accessible to anyone outside of the trial unless permission has been granted. When the information is no longer needed, it should be destroyed. It is good practice to have no identifying information on any samples collected or study document (such as questionnaires). This can be done by assigning a code for each study participant in order for their identity to be protected. The document linking participants to their study code should only be kept if follow-up contact is required and stored securely if required. Consent documents containing participant's personal information should also be kept separate from information gathered during the study. This procedure is also appropriate for the documentation of any non-written consent process (e.g. field notes). The institution, where the trial is being held, should have

policies in place to determine who has access to personal information about participants throughout the clinical trial. This may include conditions for audits or monitoring of the clinical trial.

All data collected throughout the clinical trial must also be kept under lock and key. Data stored electronically or online must be encrypted and password protected. If data collected will be used in publications, the participant must be informed of this during the consent process. Participant identifiers must never be published unless the participant has specifically consented to the publication. In the event there is a breech in the storage of data or confidential information, the reputation and respectability of the institution as well as clinical research as a whole will be negatively affected.

14.5 The Monitoring Process and Subject Protection During Clinical Trial

Throughout the clinical trial, the rights and well-being of human subjects are also protected through the monitoring process. Clinical trials are monitored for accuracy of the data collected and to ensure GCP guidelines and applicable regulatory requirements are followed. A monitor is selected by the sponsor of the clinical trial to ensure that the study is conducted in compliance with the currently approved protocol or amendments. The monitor will have knowledge of the clinical trial protocol and should have scientific and/or clinical knowledge needed to monitor the trial adequately. Monitoring occurs from the start of the study to evaluate the clinical site, personnel involved in the trial and study documents, throughout the trial, as well as at the time of closure. The monitoring process is a protective factor in the well being of the human participants as they ensure that all safety measures outlined in the protocol are followed.

14.6 Clinical Trial Registration

Clinical trials must be registered in a publicly accessible database before the first subjects are recruited such as the US-based ClinicalTrials.gov and the UK-based International Standard Randomized Controlled Trial Number Register. The general public around the globe has become distrusting of clinical research [16], particularly with some recent high profile cases of scientific misconduct, which has led to the perception that professional integrity on the part investigators and clinicians has deteriorated [17]. Such public misperceptions can impact on clinical trial enrollment and thus hinder innovation. Therefore, restoration of the public trust as well as transparency can be obtained through clinical trial registration. Accordingly, clinical trial registration promotes patient protection and benefit, advances the trust of everyone and is required [17].

14.7 Ending Trials Early

Consideration for terminating a trial prematurely is also related to patient protection. If participants experience adverse effects or if there is clear evidence that the risk to the patient outweigh the benefits, the institutional review boards and monitors can recommend that the trial be stopped early.

14.8 Concluding Remarks

The Declaration of Helsinki offers the best and most effective protection of clinical trial participants, especially in developing countries. The primary role of ethics committees is to uphold ethical principles in order to ensure a high level of protection of individuals that consent for participation in a clinical trial. Approval of a clinical trial is the responsibility of the ethics committees, and is based on the trial design and the way it is reported as well as criteria laid out for the protection of subjects taking part in the clinical trial. An important requirement for the protection of clinical trials subjects in developing countries is transparency on the trial existence, design, protocol as well as the data. The lack of information on clinical trials prospectively, as well as those in progress or even completed in developing countries is presently a major obstacle. A solution to this issue may be to implement a database accessible by the public domain that will ensure that the sponsor and the investigator conduct clinical trials in accordance to ethical principles. Governments and industry leaders are making considerable investments in transforming basic science discoveries into clinical applicability, so-called bench-to-bedside. This will increase the demand for human participation in clinical trials. Accordingly, by ensuring patient protection, the integrity and quality of the clinical trial, and that clinical trials are safe and more transparent; this increased demand will be fulfilled. This will benefit medical science and innovation.

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