Successfully Navigating the Human Subjects Approval Process

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Introduction

In order to successfully navigate the human subject approval process in clinical or behavioral research, one needs a good understanding of the ethical principles guiding the conduct of research involving human subjects. Federal and international codes and guidelines exist which frame the context of ethical research. These codes and guidelines include The Nuremberg Code (1949), the Declaration of Helsinki (1964-2000), The Belmont Report (US, 1979), Council for International Organizations of Medical Sciences (CIOMS) and/ World Health Organization (WHO) International Guidelines (1993, 2002) and the ICH/GCP International Conference on Harmonization – Good Clinical Practice (EU, 1996).

There are three ethical principles that guide all research involving human subjects – beneficence, justice and respect for persons. (Belmont Report, CIOMS/WHO).

- Beneficence refers to the ethical obligation to maximize benefits and minimize harm. In effect 'do no harm'. Assessment of risk falls under this principle. Risk in this context is defined as the probability that certain harm will occur to subjects from participation in research. It is the obligation of investigators to minimize this potential by selecting optimal study designs and interventions for their research.
- Justice is the ethical obligation to treat each person (population) equitably and equally. In this principle, distribution of the benefits and burdens or risks of research to participants and populations should be distributed fairly among diverse populations. Justice protects the vulnerable populations from exploitation and protects of the rights and welfare of vulnerable persons.
- Respect for Persons incorporates two ethical considerations – respect for autonomy and protection for persons with reduced autonomy. Autonomy refers to a person's ability to make sound decisions. In research, an autonomous person must be able to consider the potential harms and benefits, analyze the risks associated with the proposed research and make a decision in his own best interest. This includes the ability to read and understand the informed consent document.

In 2000, Emmanuel et al proposed a framework of seven ethical principles for clinical research studies, believing that informed consent is not sufficient to ensure ethical research. Expanding on the three basic principles described above, this framework adds the principles of social or scientific value – meaning that some enhancement of health or knowledge must be derived from the research and scientific validity, that the proposed research has a rigorous scientific methodology including statistical tests that produce reliable and valid data.

In the U.S., the Office of Human Research Protections (www.ohrp.gov) in the Department of Health and Human Services provides leadership and structure for overseeing the rights and welfare of subjects participating in research conducted by or supported by the US Department of Health and Human Services (HHS). These guidelines and policies are published in the Code of Federal Regulations (CFR) 45 CFR part 46. The Food and Drug Administration (FDA) regulates human subjects in clinical investigations involving drugs, biological products and medical devices. FDA regulations are published in 21 CFR parts 50, 56, 312, and 812, covering not only protection of human subjects, but also regulations for Institutional Review Boards (IRB) and other areas in the review process.

Most academic institutions have ethics or human subjects committees that review proj-

ects involving the participation of human subjects as research subjects for both behavioral and interventional studies. Independent, central IRBs also exist to serve those companies or investigators not affiliated with an academic or medical institution. IRBs such as the Western Institutional Review Board (www.wirb.com) and The New England Institutional Review Board (www.neirb.com) may review pharmaceutical or clinical protocols for studies conducted in private practice.

Is it research? A first step in determining the need for IRB review is to decide if in fact the proposed project is research and then if it is research involving humans. The US Office for Human Research Protection (OHRP) provides a series of decision trees to assist investigators in understanding human subject regulations (http://www.hhs.gov/ohrp/policy/checklists/index.html). These decision trees list the categories under which a research project may be exempt from IRB review and are a good resource for the investigator in planning for IRB review. Exempt categories for research can include research involving educational tests, survey procedures or observation of public behavior, and research involving the collection or study of existing data, documents, records or pathological or diagnostic specimens. A primary reason for the exemption is that the subjects involved in the research cannot be identified, meaning there are no personal identifiers that can link the data back to the research subject. IRB submission is still required and final determination of exemption is decided by the IRB, or in some institutions this determination is made by the Scientific Review Officer.

It is the responsibility of the IRB to review non-exempt research proposals prior to the start of any human involvement in the research. An IRB has the authority to approve, require modifications or disapprove all research activities. (§45 CFR 46.109)

- Approval: If the IRB has approved the research involving human subjects, the research may commence once all other organizational and/or local approvals have been secured. IRB approval is granted for a limited period of time, not exceeding one year, which is noted in the approval notification letter.
- Requires Modification(s): If the IRB requires modifications to secure approval, the notification letter will outline specific revisions to the Human Research protocol and/or study materials, e.g., consent form. Human Research may not commence until the IRB grants final approval. If the Principal Investigator accepts the required modifications, s/he should submit the revised materials to the IRB within the timeframe specified. If all requested modifications are made, the IRB will issue a final approval notification letter after which time the Human Research can begin.
- Deferral/Disapproval: If the IRB defers or disapproves the Human Research, the IRB will provide a statement of the reasons for this decision. Deferral or Disapproval means that the Human Research, as proposed in the submission, cannot be approved and the IRB was unable to articulate specific modifications that, if made, would allow the Human Research to be approved. In most cases, if the IRB's reasons for the deferral or disapproval are addressed in a modification, the Human Research can be approved. In all cases, the Principal Investigator has the right to address his/her concerns to the IRB directly at an IRB meeting and/or in writing.

One of the major areas assessed by the IRB when reviewing a research protocol is the potential risk to the subjects from their participation. As mentioned previously, when discussing the ethical principle of Beneficence, it is incumbent on the investigator to minimize potential risk. Some research will by its nature involve more that minimal risk. In this instance, a risk/benefit analysis is presented to the IRB to assist the review process. A second focus of IRB review is the informed consent document. This document is assessed to ensure it contains the elements for consent as determined by the regulations and ethical guidelines: purpose of the study, risks and benefits associated with participation, alternatives to participation, confidentiality, compensation, a statement of the right to refuse participation at any time without penalty and a person to contact if they have questions about their participation or the research. In addition, the consent should be written in such a manner that it is understandable by a person that can read at the 8th grade level in their native language.

Human Subject Protection Training serves as the initial guidance for new investigators conducting research involving human subjects.

Institutions provide this training and there are online courses available as well. Documentation of Human Subject Protection Training by the investigator and those involved in the project is needed for submission to the IRB. This training provides the investigator with a basic understanding of the current regulatory and ethical information. Topics include: basics of IRB regulations and the review process, assessing risk to participants, avoiding group harms, conflicts of interest, and cultural competence. Also included is information on FDA-regulated research, genetic research, HIPAA-regulated research, informed consent, international research, Internet research, records-based research, research in schools, research with protected populations, and research with vulnerable subjects, unanticipated problems and reporting, and students in research. Web-based training can be found from the NIH (https://phrp.nihtraining.com) and private educational sites such as the Collaborative Institutional Training Initiative at the University of Miami (CITI)(www.citiprogram.org).

Often considered daunting, obtaining review from an IRB for research involving human subjects can be a collaborative effort. The IRB can provide guidance and direction to the investigator to conduct valuable research with the subject's welfare and wellbeing at the forefront.

References

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