PROTECTION OF HUMAN SUBJECTS

3.1 PROTECTION OF HUMAN SUBJECTS

Background

The protection of human research subjects require that the evaluation of research applications that involve human subjects, take into consideration the risk to subjects, the adequacy of protections against risk, potential benefits of the research to subjects and others, and the importance of the knowledge to be gained. NHG Health DSRB policies and guidelines specify that reviewers should take into account, in determining overall impact that the project in the application could have on the research field involved the adequacy of the proposed protection for humans. Therefore, reviewers should evaluate the proposed plans to protect human subjects from research risks, as appropriate for the research proposed, as one of the review criteria that factor into the evaluation of scientific and technical merit. In addition to NHG Health DSRB, institutional and regulatory authorities regulations on the protection of human research subjects, there are policies set in place that require Clinical Trial applications to include a data and safety monitoring plan and for Phase III clinical trials to also have in place a data and safety monitoring board to monitor complex or potentially risky studies.

Did you know?

For Principal Investigator (PI) -initiated trials, data and safety monitoring should be performed by the PI and his/her team of Co-Investigators.

Definition of Research and Human subjects

Research is defined generally as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge." It includes activities which meet this definition, whether or not conducted under a program considered "research" for other purposes. If an activity follows a deliberate plan whose purpose is to develop or contribute to generalizable knowledge, such as an exploratory study or the collection of data to test a hypothesis, it is research. A human subject refers to a living individual about whom an investigator (whether professional or student) conducting research obtains:

- Data through intervention or interaction with the individual, or
- Identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject.

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

3.2 ETHICAL PRINCIPLES GUIDING HUMAN SUBJECT RESEARCH

Ethical Principles Guiding Human Subjects Research

Documents such as the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report articulate fundamental ethical principles that represent the framework for the conduct of human subjects research. Researchers should be familiar with the three foundation principles of the Belmont Report: respect for persons, beneficence, and justice. Closely related to these principles is the concept of informed consent, which is crucial to conducting human subjects research responsibly.

Respect for Persons

Respect for persons refers (in part) to the ethical obligation to uphold autonomy, that is, the right of competent individuals to make decisions about their own lives. According to the Belmont Report, "To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others." Respecting autonomy requires, for example, that a researcher honor the decision of a potential subject who refuses to participate in a research protocol. OHRPP provides guidance for researchers if they are seeking to enroll subjects with diminished autonomy, such as children.

Beneficence

Beneficence obligates researchers to protect and uphold the well- being of others. According to the Belmont Report, beneficence requires one to "do no harm" and "maximize possible benefits and minimize possible harms" Beneficence further means that researchers are responsible for weighing the risks of a protocol against its potential benefits. Researchers must design protocols that expose subjects to the least risk possible. Being beneficent may, for example, require that a researcher cease work with a specific subject or halt an entire protocol if a subject has been harmed.

Justice

Justice calls for benefits and burdens to be distributed fairly. Justice might require researchers to develop a strategy for ensuring that subjects, or perhaps the population from which research subjects were drawn, receive a fair share of the benefits stemming from the research. According to the Belmont Report, "An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly." For example, because it is easy to recruit a particular subset of the population for a protocol, excluding other potential groups cannot be justified. All researchers have an obligation to treat human subjects in a respectful and honest manner, which includes obtaining proper consent from potential subjects before a protocol starts.

Informed Consent Process

Conducting research on human subjects in a responsible manner usually requires that informed consent, or what is often referred to as valid consent, has been obtained from potential subjects. Three fundamental components of informed consent are:

- Subjects must be adequately informed about the research protocol in which they are being asked to enroll, including being notified about the potential benefits and risks that may be associated with participation.

- The decision of each subject to enroll must be voluntary. In other words, the subject should not be unduly influenced or coerced into making a decision about participation. Undue influence or coercion includes, but is not limited to; offering potential subjects an exorbitant amount of money for enrolling It also would include pressuring a vulnerable person such as a prisoner to enroll by offering a reduced prison sentence in exchange for participation in the research protocol.

- A subject must be competent to voice a decision about participation. The subject must be capable of understanding the information presented about the research and of appreciating the consequences of enrolling or of declining to enroll. However, in certain circumstances a non-competent individual, such as a child could participate if that child's parent or legally authorized representative approves of their participation.

The Consent Form

Obtaining consent usually occurs through a process whereby potential subjects are asked to review and sign a consent form before being enrolled in to the research. The OHRPP which oversees DSRB sets out the following considerations that must at least be included in the informed-consent document:

A statement that the study involves research, an explanation of the purpose/s of the research, the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

- A description of any reasonably foreseeable risks or discomforts.
- A description of any benefits to the subjects or to others that may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, which might be advantageous to the subject.
- A statement describing the extent to which, if any, confidentiality of records identifying the subject will be maintained and that notes the possibility that the regulatory authorities, IRB, and sponsor's monitors may inspect the records.
- Should the research involves more than minimal risk, an explanation of any compensation is provided and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject, and whom to contact in the event of complaints about research.
- A statement that participation is voluntary, that refusal to participate and withdraw from the research will not involve penalty or loss of benefits to which the subject is otherwise entitled.

A subject's consent is not valid if, for example, the researcher fails to describe adequately the risks associated with participation or if a consent form is overly technical and confusing. Because subjects in research may be vulnerable to harm, it is of the utmost importance that researchers explain the research clearly and thoroughly before the consent form is signed. This might include, but is not limited to, describing the research and answering questions in the participant's native language. Researchers also must ensure that consent forms are written at a reading level appropriate for potential subjects.

It can be difficult to determine whether the activity constitutes research on human subjects, and if so, whether a formal process for obtaining consent is necessary. In general, if the research involves human participants and can pose some non-trivial risk, it is highly likely that consent is required. It is critically important that researchers consult with the *DSRB to determine if and how guidelines for human subjects research, including those pertaining to informed consent, apply to their work. Merely complying with the law does not necessarily satisfy all of a researcher's professional obligations

when conducting research with human beings. However, researchers must fulfill obligations beyond those defined by laws or codes of ethics. They must always be mindful that their foremost responsibility is to the volunteering participants when conducting research on human subjects. The failure of researchers to protect their subjects not only risks harm to individuals and expense to them and to society, but also erodes profoundly the public's trust in research communities.

* The NHG Health Domain Specific Review Board (DSRB) is an independent committee responsible for ensuring that the research proposal protects the well-being, safety and rights of the research subjects. Research from other officials of institutions conducted under the oversight of NHG Health DSRB, may not override the decision of DSRB.

Do you know?

US FDA-regulated investigational new drug (IND) research activities cannot apply for waiver of informed consent and Exempt Review.

3.3 REFERENCES & ACKNOWLEDGMENT : PROTECTION OF HUMAN SUBJECTS

1) Australian Code for the Responsible Conduct of Research (https://www.nparks.gov.sg/avs/animals/animals-in-scientific-research/naclar-guidelines/naclar-guidelines)
2) Belmont Report (http://www.hhs.gov/ohrp)
3) British Medical Journal – Helping Doctors Make Better Decisions (Home > Volume 332, Number 7543 > BMJ 332 :677 doi: 10.1136/bmj.38797.635012.47 (Published 22 March 2006)
4) Bryn Mawr College – Ethics and Research in the Community: The Research Protocol (http://ori.hhs.gov/education/products/mass_cphs/training_staff/RCReng/RCRHome.htm)
5) Bryn Mawr College – Ethics and Research in the Community: Recruiting Participants (http://ori.hhs.gov/education/products/mass_cphs/training_staff/RCReng/RCRRecruiting1.htm)
6) Bryn Mawr College – Ethics and Research in the Community: Confidentiality (http://ori.hhs.gov/education/products/mass_cphs/training_staff/RCReng/RCRConfidentiality1.htm)
7) Bryn Mawr College – Ethics and Research in the Community: Professionalism (http://ori.hhs.gov/education/products/mass_cphs/training_staff/RCReng/RCRProfessionalism1.htm)
8) Bryn Mawr College – Ethics and Research in the Community: Applications (http://ori.hhs.gov/education/products/mass_cphs/training_staff/RCReng/RCRApplicationsStart.htm)
9) Collaborative Institutional Training Initiative – CITI Course in Human Subjects Research and Ethics (https://www.citiprogram.org/rcrpage.asp?language=english&affiliation=100)
10) Declaration of Helsinki (http://www.wma.net)
11) Dana-Farber Cancer Institute – Research (http://www.dana-farber.org/Research/About-Clinical-Trials.aspx)

12) Dana-Farber Cancer Institute – About Clinical Trials (http://www.dana-farber.org/Research/About-Clinical-Trials.aspx)
13) The European Science Foundation – Setting Science Agendas for Europe, Member Organization Forum – Fostering Research Integrity in Europe – December 2011
14) The European Code of Conduct for Research Integrity – March 2011 (https://allea.org/code-of-conduct/)
15) The European Science Foundation – ESF Member Organization Forum on Research Integrity (http://archives.esf.org/coordinating-research/mo-fora/research-integrity.html)
16) Harvard University Research Integrity Office of the Vice Provost for Research Webpage (https://vpr.harvard.edu/)
17) International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Guideline for Good Clinical Practice E6 (R1), Current Step 4 version dated 10 June 1996. (https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf)
18) National Medical Ethics Committee - Ethical Guidelines on Research Involving Human Subjects (http://www.moh.gov.sg)
19) Journal of Empirical Research on Human Research Ethics Notes, Concepts, Tools and Resources for Solving Ethical Problems in Human Research : What to Share and What to Redact: Protecting Confidentiality while Preserving Usefulness
20) Journal of Empirical Research on Human Research Ethics Notes, Concepts, Tools and Resources for Solving Ethical Problems in Human Research : Evaluating Vulnerability in Research Participants (https://www.researchgate.net/journal/1556-2646_Journal_of_Empirical_Research_on_Human_Research_Ethics)
21) Journal of Empirical Research on Human Research Ethics Notes, Concepts, Tools and Resources for Solving Ethical Problems in Human Research : Public Disclosure Regarding Emergency Research (https://www.researchgate.net/journal/1556-2646_Journal_of_Empirical_Research_on_Human_Research_Ethics)
22) National Institute of Health - NIH Guide (https://www.nih.gov/research-training/safety-regulation-guidance)

23) National Institute of Health, Office of Extramural Research – Introduction: Protection of Human Research Participants (http://phrp.nihtraining.com/introduction/01_intro.php)
24) Office of Research Integrity – Introduction to the Responsible Conduct of Research: Planning Research, The Protection of Human Subjects (https://ori.hhs.gov/ori-introduction-responsible-conduct-research)
25) Office of Research Integrity – Introduction to the Responsible Conduct of Research: Planning Research, Federal Regulations (https://ori.hhs.gov/ori-introduction-responsible-conduct-research)
26) Office of Research Integrity – Introduction to the Responsible Conduct of Research: Planning Research, Definitions (http://ori.dhhs.gov/education/products/RCRintro/)
27) Office of Research Integrity – Introduction to the Responsible Conduct of Research: Planning Research, IRB Membership and deliberations (https://ori.hhs.gov/ori-introduction-responsible-conduct-research
28) Office of Research Integrity – Introduction to the Responsible Conduct of Research: Planning Research, Training (https://ori.hhs.gov/ori-introduction-responsible-conduct-research)
29) Office of Research Integrity – Introduction to the Responsible Conduct of Research: Planning Research, Continuing responsibility (https://ori.hhs.gov/ori-introduction-responsible-conduct-research)
30) Office of Research Integrity – Introduction to the Responsible Conduct of Research: Planning Research, Ethical Issues (https://ori.hhs.gov/ori-introduction-responsible-conduct-research)
31) Office of Research Integrity – Policies - Statutes and Regulations (https://ori.hhs.gov/ori-introduction-responsible-conduct-research)
32) International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Guideline for Good Clinical Practice E6 (R1), Current Step 4 version dated 10 June 1996. (https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf)The European

Science Foundation – Setting Science Agendas for Europe, Member Organization Forum – Fostering Research Integrity in Europe – December 2011

33) The European Code of Conduct for Research Integrity – March 2011(https://allea.org/code-of-conduct/)

34) U.S. Department of Health and Human Services, Office of Human Research Protection, International: 2011 Edition of the Compilation of Human Subjects Protection (http://www.hhs.gov/ohrp/international/)

35) U.S. Department of Health and Human Services, Office of Human Research Protection, Code of Federal Regulations (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html)

36) U.S. Food and Drug Administration - CFR - Code of Federal Regulations Title 21 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm)

37) University of California Regents – Teaching the Responsible of Conduct of Research in Humans (RCRH): Research in Humans (https://ori.hhs.gov/education/products/ucla/default.htm)