Responsible Conduct of Human Studies

Introduction

All research and some innovative diagnostic and therapeutic activities that will involve human subjects whether directly or indirectly must be reviewed and approved by the Human Research Committee prior to their initiation. The Committee's procedures and the requirements for review and action are contained in Partners Human Research Committee Goverance and Operating Procedures. This is available for investigators from the Partners Human Research Office and should be consulted prior to the preparation of protocols and consent forms for review.

Under our Multiple Project Assurances (MPAs), the Partners institutions have made a commitment that all human research conducted within the Partners HealthCare System or by a Partners investigator will be performed in compliance with all applicable local, state and federal regulations, the latter being known as the "Common Rule" (Title 45 Code of Federal Regulations Part 46).

When conducting clinical research, an investigator's actions should be guided by the three fundamental ethical principles for human research identified in the Belmont Report: respect for persons, beneficence and justice. Every investigator should read and understand the principles set forth in the Belmont Report prior to participating in any human research.

Every investigator and member of a research team should know the following information about the responsible conduct of clinical research before participating in any research involving human subjects.

Definition of Human-Subject Research

- **Research** is defined as a systematic investigation, including research development, testing and evaluation (i.e., pilot studies), designed to develop or contribute to generalizable knowledge.
- **Human subject** is defined as an individual about whom an individual (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information or specimens.
- **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). **Research limited to the use of non-identifiable patient information may qualify for exemption from HRC review; however all exemptions must be granted by the Human Research Office.**

Designing an Ethical Research Study

- Human studies may be of direct benefit to the participants, whether patients or volunteers, or the studies may be of no direct benefit to the individual participants but may ultimately be of help to others as well as contribute to the advancement of scientific knowledge. One of the most important components of such studies is that informed consent be given by or for all participants.
- A human study should be well-designed according to sound scientific principles and be preceded by adequate laboratory and/or animal studies. A study which will not yield valuable data is unacceptable.
- A study is ethical or not at its inception; it does not become ethical because it succeeds in producing valuable data.

- A study should not be undertaken unless the risks and hazards are believed to be predictable.
- The gain anticipated from a human experiment must be commensurate with the risk involved. Risks and hazards to be evaluated include the possibility of physical, psychological, sociological, or other harm that might be incurred as the consequence of a research activity. Sometimes large risks are taken for large gains in human knowledge, but in almost all cases such large risks should be taken only when an individual is likely to benefit directly in needed diagnosis or therapy. In all human research, concern for the individual takes precedence over the interests of science and society.
- When children under the age of 18 or others unable to give consent for themselves are sought as subjects, there should be essentially no identifiable risk associated with participation in the study. If there is any risk, it must be decisively outweighed by potential benefits to the subjects.
- Investigators should not take undue or unusual risk with themselves in self-experimentation, but should exercise the same prudence and judgment as they would in studies of others.
- The controlled clinical trial in diagnosis and therapy is permissible under ordinary circumstances only when there is uncertainty as to which of two procedures is better.
- The study design should minimize risk to the subjects and maximize benefits. The use of placebo controls must be scientifically based and ethically justifiable; in such studies, special precautions must be taken to ensure that no patient/subject will be denied effective therapy when one is known to exist.
- It is preferable to have at least two professionally qualified persons involved in experimental situations. Conflicts of concern for the welfare of the patient and of interest in the experimental study can arise when the personal physician or the investigator attempts to encompass both roles alone. Similarly, a controlled clinical trial, in which experimental and control groups are compared, is best supervised by two or more investigators rather than by one investigator.
- When difficult ethical problems arise, it is often helpful for them to be presented to a group of the investigator's colleagues as well as to the Human Research Committee for discussion and advice.

Informed Consent

1. Prior to beginning a human study, it is essential to obtain the informed consent of the individual involved, whether it be a patient or a healthy volunteer. Informed consent is an expression of the willingness of a person to participate as a subject in a research or experimental activity. Such consent must be freely given, without coercion, and must be based on a clear understanding of the nature and purposes of the study and the factors involved in participation. Firm application of the **Golden Rule** would go far to eliminate difficulties here.
2. It is the investigator’s responsibility to ensure that proper informed consent is obtained from every subject according to procedures approved by the Human Research Committee; this responsibility cannot be delegated.
3. Communication between subject and investigator should embody aspects similar to those in a good patient-doctor relationship. The discussion with the potential participant by the investigator or co-investigator should include the purpose of the research, the procedures to be followed, and the discomforts, risks, and possible benefits, if any. The signing of the consent document should signify that thorough discussion has taken place and will continue to take place during the conduct of the study.
4. Patients being asked to participate in diagnostic or therapeutic trials should be informed of any alternative choices for diagnosis or treatment. All subjects should know if their treatment is to be determined by random selection and if placebos are to be used. No information should be withheld that might influence the decision, nor should there be promises of beneficial results.
5. The patient or volunteer should feel at liberty to refuse to join the study, or to discontinue participation at any time, without prejudice to his/her present or future care.
6. The same principles that pertain to obtaining informed consent from patients and healthy volunteers should also be applied by investigators in making a request for consent from parents, next-of-kin or legally authorized representatives of those unable to give consent for themselves due to minor age, physical incapacity or mental incompetence. In such cases a subject advocate may be appointed. When a subject advocate is appointed, the subject advocate is expected to act in the best interests

of the subject by sharing in discussions with the investigator and with those responsible for giving consent.

7. Although minors are unable to give consent for themselves, children of seven years or older should participate in the consent process with the view of obtaining their assent to join the study. If the study involves greater than minimal risk or discomfort and does not offer the prospect of direct benefit to the subject, the child must positively affirm his/her willingness to participate.
8. An individual's willingness to join a study must be documented by a written consent form, or, in certain types of studies as determined by the Human Research Committee, by oral consent, noted in the subject's medical record. In rare cases, the Human Research Committee may waive documentation of informed consent when such documentation might constitute a potential risk to the subject's privacy.
9. In all cases particular care must be exercised to avoid coercion to join a study, especially if the patient or healthy volunteer is in a dependent relationship to the investigator, or if monetary rewards are offered.

Selection of Research Subjects

1. An investigator should be aware of the medical history of potential subjects and of previous studies in which the individuals may have participated. While hospital and physicians' records facilitate such screening of patients, particular care should also be taken in discussions with healthy volunteers to discover any information that might preclude the subject's inclusion in the study, such as past or present medical problems or participation in other research studies.
2. While studies of a captive group of subjects, such as students, laboratory personnel, and hospitalized patients may be useful and desirable and can be conducted in an ethical fashion, a scrupulous effort must be made to preserve the individual's rights because of the possibility of coercion.
3. Studies of volunteers in the investigator’s own department or who are the investigator's students should be avoided and will usually be disapproved by the Human Research Committee because of the subtle coercive factors that could be present in even the most harmonious situations.
4. In general, prisoners are not acceptable subjects for experimentation, except when participation in research provides the only prospect of receiving effective therapy for a given medical condition. Under such circumstances, extreme care must be taken to ensure that the interests of the participants are protected and that all practicable steps to eliminate coercion are taken. In such cases, the likelihood that an individual will personally benefit from participation in the research activity must be compelling and outweigh the attendant risks.
5. Investigators conducting studies of patients in the Emergency Department must observe the same ethical considerations required in other areas of the hospital. If a patient in the Emergency Department is unable to give consent, the study must be of potential benefit to the patient and consent must be obtained from the next-of-kin or legally authorized representative before the patient is entered into a study. Informed consent cannot be obtained retroactively from a patient.
6. Multiple studies of the same individual, which are of no direct benefit to that individual, should be avoided. Subjects may unknowingly endanger their health by participation in several studies in succession.
7. Patients who are close to death or in danger of sudden death are not suitable subjects for a study, unless the investigator is convinced that the study will directly benefit the individual and improve the quality of his/her remaining life. Studies of such persons should not be made solely for the benefit of science and society.

Privacy and Confidentiality

- During the course of a study, the highest standards should be maintained with regard to the privacy and confidentiality of information including interviews, photographs and other records concerning the subject. Although more investigators and staff may be involved in the conduct of a study than might occur in the usual course of treatment of a patient, confidentiality standards, as detailed in the **Partners Privacy and Confidentiality Policies,** should not be relaxed.

- While the records of certain studies must be made available to the U.S. Department of Health and Human Services or the U.S. Food and Drug Administration for audit purposes and, sometimes, to a sponsoring drug company as a means of validating results, confidentiality must still be maintained and the identity of individuals disguised as much as possible through the use of code numbers, rather than names, medical records numbers, or other commonly used identifiers, such as social security number.
- The patient's right to privacy becomes directly affected in genetic and behavioral studies that require the participation of a patient's relatives or friends. The patient should be asked to obtain permission from relatives or friends to be contacted by the investigator to participate in the study. Parents or guardians of a child who is in a study should be similarly consulted before a child's siblings or playmates are approached for inclusion in a study.
- In the publication and use of investigational results, it must be made unmistakably clear that the all ethical and privacy proprieties have been observed in the study. One of these proprieties is adequate disguise of the identity of the subject in text and photographs. Every effort must be taken to protect the privacy and anonymity of individuals in the report, as well as during the study.
- Because of the uniquely personal and predictive nature of an individual's genetic information, disclosure may have serious psychological, social and economic consequences. Great care must be taken to ensure that confidentiality of genetic information is maintained and that the individual’s right to determine who has access to such information is respected and preserved.

Proper Conduct of a Study

- A research study cannot be initiated until all required documentation has been completed and it has been fully approved by the Human Research Committee.
- A research subject’s participation in the research study cannot be initiated until the informed consent process has been completed and documented in writing on a valid current version of the consent form.
- A subject is considered enrolled in the study once the informed consent process is completed and consent has been documented. Enrollment of subjects in excess of the number approved by the Human Research Committee is not permissible.

- Only patients or volunteers who meet all eligibility criteria should proceed on study. Any exceptions to the eligibility criteria in the approved protocol must be reviewed and approved by the Human Research Committee.
- Any deviation from the approved protocol must be reviewed and approved by the Human Research Committee prior to implementation except when changes must be made immediately to protect the well-being of the research subject(s). All protocol deviations must be reported immediately to the Human Research Office.
- All adverse events experienced by a research subject must be reported to the Human Research Committee whether or not they are considered by the investigator to be related to the research itself. The Human Research Office must be notified immediately of any serious adverse events, and a full report must be filed within ten working days of the event.
- All case report forms and data collection sheets should be completed accurately and should be signed and dated by the individual recording the information. All data should be recorded in ink, any changes or corrections should be made by a single strike through which makes it possible to read the original entry, and the change should be dated and initialed by the individual making it.
- All original source documents and case-report forms should be retained for a minimum of three years after completion of the study. The FDA has specific records retention requirements for studies involving Investigational New Drug (IND) drugs or Investigational Device Exemption (IDE) devices. Consult the FDA regulations and/or the sponsor and retain records in accordance with stated requirements.
- There can be no additions or modifications to an approved consent form without prior approval from the Human Research Committee.
- All members of the research team must be properly trained and qualified to perform the tasks they are assigned.

- All members of the research team share responsibility for ensuring the safety and well being of the research subjects throughout the course of the study.

- A subject's continuing participation in a study must be voluntary.

Monitoring of Studies

1. The Chief of Service/Department, as well as the investigator, is responsible for assuring that the conduct of the study follows the approved protocol, and that the investigator abides by the decisions and procedures of the Human Research Committee.
2. The Human Research Committee continually monitors ongoing human research studies and is required to conduct a complete and substantive review of every protocol at least annually as part of its responsibilities for protecting the rights and welfare of participants in the research studies.
3. When a study is suspended or cancelled due to adverse reactions to a drug, procedure or mechanical device, the investigators should also inform the participants in the study of the reasons for the suspension or cancellation.

Termination of a Study

- A study should be discontinued when hazards to the subject are found to be greater than anticipated, or when one treatment appears clearly to be less effective than another with which it is being compared. Patients should not be denied the benefits of the more effective treatment, once its value has been established.
- A study should be deemed completed when a sufficient number of patients or healthy volunteers have been studied and valid information obtained.

Emergency Use of Investigational Drugs or Devices

1. The FDA allows for the emergency use of an investigational drug or device without prospective HRC approval when the patient has a disease or condition that is life-threatening or severely debilitating, the patient’s disease or condition requires intervention with the investigational drug or device, and no alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the patient’s life, and time is not sufficient to obtain HRC approval.
2. Informed consent must be obtained from the patient or the patient’s legally authorized representative unless the patient is unable to communicate and time is not sufficient to gain consent from the patient’s legal representative.
3. An institution is permitted ONE emergency use of an investigational drug or device without prospective HRC approval. Under FDA regulations, all additional uses of the investigational drug or device should be anticipated and must be performed under an HRC-approved protocol.
4. Emergency uses of an investigational drug or device must be reported to the HRC immediately, followed by a full report within 5 working days.
5. All other uses of investigational drugs or devices require prospective review and approval of the HRC.