Guide for Human Subjects Research at the University of Iowa
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Guide for Human Subjects Research at the University of Iowa

Scope: This document provides information on human subjects research policies and is intended for use by investigators, researchers, Institutional Review Board members, members of other UI committees, other UI administrators or others who are involved with research that involves human participants.

Chapter 1 -- Introduction to the IRB and Human Subjects Office

The University of Iowa operates a centralized program to review and approve all research involving human subjects through the Office of the Vice President for Research. Before a research project involving human subjects is initiated, it must be reviewed and approved by an Institutional Review Board (IRB). While the principal investigator has primary responsibility for the conduct of the study, the University of Iowa IRBs are responsible for protecting the rights and welfare of study participants. Through its Federalwide Assurance, the University is held accountable to federal agencies that have established guidelines for the use of human subjects in research.

The University of Iowa Human Subjects Office (HSO), located at 340 CMAB, has several functions:
- To provide administrative support for two Institutional Review Boards
- To provide assistance to investigators who are preparing IRB applications
- To process applications as efficiently as possible
- To maintain records of IRB reviews and approvals
- To coordinate submissions to the Western Institutional Review Board (WIRB)
- To maintain documentation of the facilitated reviews of the NIH National Cancer Institute’s Central IRB (CIRB)

Other Administrative Offices for Researchers with External Support

In addition to the IRB review process, all human research with external support (funds, drugs, or devices) must be processed through one of two other University administrative offices, depending on the source of support:

(1) For projects with government, foundation, or voluntary health agency support:
The Division of Sponsored Programs (www.research.uiowa.edu/dsp)
100 Gilmore Hall
Note: Funding is not released until IRB approval has been obtained for the project.

or

(2) For projects with corporate support:
The Clinical Trials Office (www.research.uiowa.edu/cto)
340 College of Medicine Administration Building
Note: IRB approval is not released to investigators until the contract has been finalized.

The Division of Sponsored Programs and the Clinical Trials Office review and provide institutional sign-off for all research projects, including negotiation of contracts if applicable. Also, these offices notify the Grant Accounting Office to establish research accounts.
Chapter 2 -- Foundation of Human Subjects Protection

The National Research Act of 1974 established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission was charged with identifying the basic ethical principles that should underlie research with human subjects. Members of the Commission were from diverse disciplines, including medicine, law, religion, and bioethics. In 1979 the Commission published its report, Ethical Principles and Guidelines for the Protection of Human Subjects of Research, commonly called the Belmont Report. Today's federal regulations for the protection of human subjects are based on the ethical principles of the Belmont Report. The Belmont Report identifies three basic principles as particularly relevant to the ethics of research involving human subjects.

A. Respect for Persons

The principle of respect for persons means respecting an individual's autonomy (his/her right to make decisions for him/herself). This means that individuals should participate in research voluntarily and be given enough information to make an informed decision about whether or not to participate.

"To respect autonomy is to give weight to autonomous persons' considered opinions and choices... To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information ... when there are no compelling reasons to do so."

The Belmont Report further specifies that persons with diminished autonomy (e.g., children, cognitively impaired persons) are entitled to protection.

The principle of respect for persons is embodied in the informed consent process. Three elements crucial to the informed consent process are information, comprehension, and voluntariness. While there is no standard for the amount of information to be provided to potential volunteers, the Belmont Report suggests that "the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge."

The way in which information is provided to the volunteer is as important as the information itself. The investigator should adapt the presentation of information to the subject's level of understanding. When a subject's comprehension is limited due to immaturity or mental disability, respect still requires that the person be given the opportunity to choose whether or not to participate to the extent they are able. Permission from a third party who understands the subject's situation and can act in the subject's best interest further protects the subject from harm.

Finally, in order to be voluntary, consent must be given under conditions that are free of coercion and undue influence. "Unjustifiable pressures usually occur when persons in positions of authority or commanding influence ... urge a course of action for a subject." Consent is valid only if the agreement to participate in the research is given voluntarily.

B. Beneficence

The principle of beneficence requires that the investigator not only protect individuals from harm, but make efforts to secure their well-being.

"Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms... The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks."
Risks to subjects may be balanced against the benefits to subjects directly or to society as a whole.

When the investigator and the IRB perform a systematic risk/benefit assessment, they are applying the principle of beneficence. Risk is evaluated by considering both the chance or probability of harm and the severity or magnitude of the possible harm. Risk may include consideration of psychological, physical, legal, social, and economic harm. Benefit, on the other hand, is the anticipated positive value of the research to either the subject directly or to society in terms of knowledge to be gained.

"...the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research."

C. Justice

The principle of justice means that the benefits and burdens of the research are fairly distributed.

“For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients... In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population."

It is a violation of the principle of justice to select a class of subjects (e.g., welfare patients, an ethnic minority, institutionalized persons) simply because of easy availability rather than for reasons directly related to the problem being studied. The principle of justice requires that there be fair procedures and outcomes in the selection of research subjects.

"Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only 'undesirable' persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons."
Chapter 3 -- Scope and Purpose of Institutional Review Boards

A. Federal Regulatory Authority

The federal regulations require the establishment of an Institutional Review Board (IRB) to review and approve human subjects research prior to its initiation. These regulations also require that specific points of information be included in the informed consent process, and that, in most cases, the consent process itself be documented in writing.

The University of Iowa has filed an assurance of compliance, called a Federalwide Assurance (FWA), with the Office for Human Research Protections (OHRP) in the Department of Health and Human Services (DHHS). The University is required to enter into this agreement because it receives federal funding for research involving human subjects. An FWA is a binding written agreement between the University of Iowa and DHHS. It states that the University is guided by the ethical principles of the Belmont Report, and will comply with federal regulations (45 Code of Federal Regulations Part 46, or simply 45 CFR 46) for all federally-funded human subjects research. The Food and Drug Administration (FDA) regulations under which the IRB operate are found at 21 CFR 56.

The Federalwide Assurance describes the responsibilities of the institution, the Office of the Vice President for Research, the IRBs, and the investigator. All investigators at the University of Iowa are expected to conduct research in accordance with the provisions of the Federalwide Assurance, regardless of the funding source for their research.

The Iowa City Veterans Affairs Medical Center (VAMC) has its own FWA. The University of Iowa provides IRB review for human subjects research conducted at the Iowa City VAMC under an IRB Authorization Agreement. Projects reviewed for the VAMC receive the same IRB review as those conducted at The University of Iowa.

Primary responsibility for assuring that the rights and welfare of the individuals involved are protected rests with principal investigator conducting the research. Faculty members who assign or supervise research conducted by students have an obligation to consider carefully whether those students are qualified to safeguard adequately the rights and welfare of subjects.

B. What Needs Review by the IRB

Before a research project involving human subjects is initiated, it must be reviewed and approved by a University of Iowa Institutional Review Board (IRB).

All research involving human subjects must be reviewed by the IRB if
- the research is sponsored by the institution, OR
- the research is conducted by or under the direction of any employee or agent of this institution (including students) in connection with his or her institutional responsibilities, OR
- the research is conducted by or under the direction of any employee or agent of this institution using any property or facility of this institution, OR
- an employee or agent of this institution (including students) meet the criteria for “engaged in research” as defined in OHRP guidance of January 26, 1999 (www.hhs.gov/ohrp/humansubjects/assurance/engage.htm) OR
- the research involves the use of this institution's non-public information to identify or contact human subjects.
At the University of Iowa, “Human Subjects Research” is defined as an activity that either:
• Meets the DHHS definition of “research” and involves “human subjects” as defined by the DHHS regulations; OR
• Meets the FDA definition of “research” and involves “human subjects” as defined by FDA regulations.

1. What is Research?

**DHHS Definition of Research**

DHHS regulations define research as a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research even if they are a component of a larger non-research activity (e.g., instruction, demonstration).

**FDA Definition of Research**

FDA defines research as any experiment that involves a test article and one or more human subjects and that is one of the following:
• subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or
• is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit.
• The term does not include experiments that are subject to the provision of 21CFR58, regarding nonclinical laboratory studies. (From 21 CFR 50.3(c); 21 CFR 56.102(c))

Under FDA regulations, the terms “research” and “clinical investigation” are synonymous.

**What is a test article?**
A test article means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the Federal Food, Drug & Cosmetic Act. [21 CFR 50.3(j)].

For drug studies, FDA defines a clinical investigation as any experiment in which a drug is administered or dispensed to, or used involving one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice. [21 CFR 312.3(b)] (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.3)

For device studies FDA defines an investigation as a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device. [21 CFR 812.3(h)] (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.3)
2. Who is a Human Subject?

DHHS Definition of a Human Subject

DHHS regulations define a human subject as a living individual about whom an investigator (whether professional or student) conducting research obtains either:

(a) data through intervention or interaction with the individual, OR
(b) identifiable private information.

What characterizes an intervention with an individual?

Intervention includes both physical procedures by which data are gathered (e.g., drawing blood) and manipulations of the subject or the subject's environment that are performed for research purposes.

An example of such an intervention would be an educational intervention such as randomly providing pamphlets to some patient-subjects that provide tips for sticking to medication regimens while not providing that information to a set of other patient-subjects with the intent of testing the effectiveness of such a program on increasing compliance with medication schedules. This type of project involves human subjects because there is an intervention (handing out educational pamphlets) with living individuals.

What characterizes an interaction with an individual?

Interactions include communication or interpersonal contact between investigator and subject.

An example of an interaction with a human subject could be a blood draw or finger stick for research purposes. In this case, there is an interaction with a living individual that is being done outside of the realm of regular patient care.

What is private information?

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 (e.g., medical record information).

Private information must be individually identifiable (i.e. the identify 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.

Obtaining identifiable private information means receiving or accessing identifiable private information or identifiable specimens for research purposes. “Obtain” includes an investigator’s use, study, or analysis for research purposes of identifiable private information or identifiable specimens already in the possession of the investigator. In general, private information or specimens are individually identifiable when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

“Coded” in this sense means that:

a) identifying information (such as name or social security number) that would enable the investigators to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, and/or combination thereof.
(i.e., the code); AND
b) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

What defines a “living” individual?
Since the definition of a human subject is a “living” individual, research which only involves only autopsy materials, cadavers or death records is not considered human subjects research and is not reviewed by the IRB.

FDA Definition of Human Subject
FDA regulations define human subject as an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient. For research involving medical devices, a human subject is also an individual on whose specimen an investigational device is used.

3. How do I know if my project is research involving human subjects?

The University of Iowa Chairs or HSO staff provide guidance and determination with regard to when an activity meets either the DHHS definitions for human subjects research or FDA definitions for clinical investigation with human subjects. Requests for determinations may be submitted to the Chairs or HSO staff either verbally or in writing and the Chairs or HSO staff may respond either verbally or in writing with a determination.

If you have questions about whether or not your project meets the definitions of research involving human subjects and requires IRB review, call the HSO office at (319) 335-6564 or send us an email at irb@uiowa.edu.

C. University of Iowa Institutional Review Boards

There are two Institutional Review Boards at the University of Iowa. Both IRBs review and approve research in accordance with Department of Health and Human Services (DHHS) regulations at 45 CFR 46. In addition, for studies involving products regulated by the Food and Drug Administration (FDA) regulations, the University of Iowa IRB-01 complies with the requirements set forth in 21 CFR 11, 21 CFR 50, 21 CFR 56, 21 CFR 312, and 21 CFR 812 and 21 CFR 814, Subpart H. When research involving products regulated by the FDA is funded, supported or conducted by FDA and/or DHHS, both the DHHS and FDA regulations apply.

1. IRB-01 (Biomedical)

Any research project involving human participants, regardless of its source of funding, is reviewed by IRB-01 if:

- the Principal Investigator (PI) is from the College of Dentistry, Medicine, Pharmacy, Public Health, or the Department of Speech Pathology and Audiology in the College of Liberal Arts.
- the PI is from the College of Nursing and the study involves a physical or physiological intervention that is greater than minimal risk, OR
- the study involves access to or creation of any protected health information about the subject that is maintained in a health care provider's records.

The chair may, at his/her discretion, refer the review of a research project to IRB-02 if he/she determines
(a) there is a conflict of interest among the investigator(s) and board member(s), OR
(b) there is more appropriate expertise on the other board.
Exceptions: Research projects involving the VAMC, FDA-regulated research or that include physical or physiologic interventions involving more than minimal risk may not be referred to IRB-02 for review. For these projects, when there is a conflict of interest, the IRB-01 chair can assign the project to a non-conflicted member of the IRB or, in the case of a potential conflict with more than one member of an assembled full board, the chair can re-schedule the project to a future meeting where there are no conflicts of interest. For these projects, when the IRB-01 chair determines the need for more appropriate expertise, the chair can invite a consultant with more appropriate expertise to review and present the project to the IRB-01 membership.

IRB-01 meets every Thursday (primarily for new project reviews and modifications) and every other Monday (continuing reviews). More information about IRB-01, including the current chairs and roster (list of members), is available by clicking on the following link, IRB-01.

IRB-01 is also convened on an “as-needed” basis for the specific purpose of reviewing reports of noncompliance, to make policy determinations, or to conduct additional project reviews. These convened full-board meetings are scheduled so that the majority of those in attendance are the rostered primary members of the board. When IRB-01 is convened in this manner, it is referred to as the IRB-01 Executive Committee.

2. IRB-02 (Behavioral/Social Science)

Any research project involving human participants, regardless of funding, is reviewed by IRB-02 if the Principal Investigator is from the College of Business, Education, Engineering, Law, Liberal Arts (except for those from the Department of Speech Pathology and Audiology), or Nursing.

EXCEPTIONS: Even if the PI is from one of the preceding colleges, IRB-01 would review the project if:
  • the PI is from the College of Nursing and the study involves a physical or physiologic intervention that is greater than minimal risk, OR
  • the study involves access to or creation of any protected health information about the subject that is maintained in a health care provider's records.

The chair may, at his/her discretion, refer the review of a research project to IRB-01 if he/she determines
  (a) there is a conflict of interest among the investigator(s) and board member(s), or
  (b) there is more appropriate expertise on the other board.

IRB-02 meets as needed on the second and fourth Wednesday of each month. More information about IRB-02, including the current chairs and roster (list of members), is available by clicking on the following link, IRB-02.

Policy issues and reports of noncompliance are reviewed during regularly scheduled IRB-02 full board meetings.

D. Non-UI Institutional Review Boards

1. National Cancer Institute (NCI) Central IRB (CIRB)

Under an IRB Authorization Agreement between the University of Iowa and the National Cancer Institute Central IRB (CIRB) (www.ncicirb.org), the CIRB provides IRB review for Phase 3 Cooperative Group adult cancer treatment protocols and selected other cancer trials conducted at the University of Iowa. A copy of this document is available upon request from the Human
Subjects Office. The primary function of the CIRB is to perform initial and continuing review of the protocol and the primary function of the University of Iowa is consideration of the local context and oversight of local performance. The University of Iowa IRB decides on a protocol-by-protocol basis whether to accept the review of the CIRB or to conduct its own review of the protocol. Please contact the HSO if you have any questions about whether or not your protocol is eligible for review by the CIRB.

The UI/HSO/CIRB procedures for investigators wishing to submit projects for CIRB facilitated review available in the Human Subjects Office. You may still require the review and approval of other UI committees prior to obtaining CIRB facilitated review of the protocol. Please call the HSO for more information.

2. **Western IRB (WIRB)**

Beginning November 1, 2005, NEW protocols that are both industry-sponsored AND industry-initiated are sent to a commercial IRB for review. The University of Iowa IRB will no longer be the IRB of record for these types of projects. The University of Iowa has contracted with the Western Institutional Review Board (WIRB) for the review and oversight of these projects conducted at the UI. No other commercial IRB review will be allowed for these projects. Projects previously approved by IRB-01 will NOT be transferred to WIRB.

All of the following conditions must apply to the research project before it will be submitted to WIRB for review:

- The project is a study that involves human subjects and is designed to evaluate prospectively the safety and/or effectiveness of new drugs or devices or behavioral interventions.
- The protocol for the project was designed and written by the sponsor.
- The sponsor holds all INDs/IDEs for the protocol.
- The only sponsor of the research is a for-profit entity/company.
- The UI investigator has not previously submitted the study to another UI IRB. Note: Only new projects starting on November 1, 2005 will be eligible to be submitted to WIRB for review. No transfers of projects already submitted to and approved by IRB-01 is allowed.
- The project does NOT involve any of the following:
  1. Xenotransplantation
  2. Embryonic stem cells
  3. Review and approval by the UI Institutional Biosafety Committee (e.g. studies that involve recombinant DNA)
  4. Any research funds from a federal or other not-for-profit funding source.

Studies that are eligible for WIRB review and oversight may not be conducted at the VAMC. The VAMC does not, at this time, allow the use of commercial IRBs for review of human subjects research at VAMC facilities.

The UI IRB has the right to decide to keep any new research protocol at the UI for review by IRB-01. This will be decided on a case-by-case basis by an IRB-01 Chair. The UI may decide to retain a protocol for IRB-01 review if the protocol has significant local context issues such as a unique vulnerable population, involves an investigative team that has had previous serious and/or continuing noncompliance issues, or if the research design or intervention adds unusual risk for the subjects. If you have questions about whether or not your protocol should be processed with the UI/WIRB procedures, please call the HSO.
If your project is designated to go to WIRB for review, there are some requirements of the UI prior to submission. First, the Clinical Trials Office must have a copy of the contract and protocol for the project. Second, if the project requires review by any UI committees, you will need to have the approvals of the applicable committee prior to WIRB review. Finally, you will need to send all of your WIRB submission materials to the UI HSO so that the UI/WIRB coordinator can check for your other committee approvals and the required UI consent language. At this point, the UI HSO is responsible for submitting your new project materials to WIRB for review. The following link will provide you a detailed description of the UI process for submission to WIRB and any required forms: UI/WIRB Procedures.

Once your new project has been sent to WIRB for review, WIRB is then the IRB of record for the project. At that point, all correspondence regarding the project will be with WIRB. In addition, after WIRB approval of the project, you will submit all modifications, continuing reviews, serious and/or unexpected adverse experiences, major protocol violations that result in additional risks to subjects, and project closure notice to WIRB using WIRB procedures. The UI HSO will not coordinate any of these submissions after the approval of the new project by WIRB. For more information on WIRB procedures, check out their website at www.wirb.com.
Chapter 4 – Categories of Review

Research projects are reviewed at a full board meeting unless the project qualifies for exempt status (see Section A of this chapter) or can be classified as minimal risk and meets the criteria for expedited review (see Section B of this chapter). The type of review depends on the risks posed to potential subjects.

What is minimal risk?

The federal regulations provide two definitions of minimal risk – one for prisoners, and another for non-prisoners (general population).

For the general population, the federal regulations define minimal risk to mean that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. [45 CFR 46.102(i) & 21 CFR 56.102(i)]

For prisoners, the federal regulations define minimal risk as the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons. [45 CFR 46.303(d)]

The definition of minimal risk serves as a starting point for the IRB chair's determination of the category of review. Risk includes not only physical risk, but also psychological, emotional, legal, social, and financial or the risk of loss of privacy or breach of confidentiality. If a project, falls into an exempt category or meets the definition of minimal risk and falls into an expedited category as described below, the IRB chairs (or his/her IRB member designee) may review and approve the project. The categories of exempt and expedited are mutually exclusive. If the research does not fall into one of the exempt categories, then the expedited review categories are considered.

A. Exempt Human Subjects Research

The University of Iowa policy requires that all human subjects research proposals be submitted for review. However, certain types of human subjects research may be classified as exempt from the federal regulations [45 CFR 46.101(b) (DHHS) and 21 CFR 56.104 (FDA)]. The IRB chair (or his/her IRB member designee) is the sole authority for determining whether the research meets the exempt criteria, based on review and approval of the investigator's New Project application to the IRB. In making this determination the IRB chair (or his/her IRB member designee) considers any ethical issues including coercion. Exempt research projects have no requirement for continuing review.

Exemptions under the DHHS regulations are limited to research activities in which the only involvement of human subjects will be in one or more on the following categories.

1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, unless:
   (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
(ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, or reputation.

3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior not otherwise exempt under category 2 above, if:
   (i) the human subjects are elected or appointed public officials or candidates for public office; OR
   (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

   NOTE: Existing data, documents, records, pathological or diagnostic specimens means the items must be “on the shelf” or in existence at the time the project is submitted to the IRB for review.

5) Research and demonstration projects which are conducted by or subject to the approval of Department or Agency heads, and which are designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payments for benefits or services under those programs.

   NOTE: For exempt research and demonstration projects, the IRB chair (or his/her IRB member designee) determines that the project:
   • Be conducted pursuant to specific federal statutory authority,
   • Has no statutory requirements for IRB review,
   • Does not involve significant physical invasions or intrusions upon the privacy interests of the subject,
   • Has authorization or concurrence by the funding agency.

6) Taste and food quality evaluation and consumer acceptance studies (i) if wholesome foods without additives are consumed; or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the FDA or approved by the EPA or the Food Safety and Inspection Service of the US Department of Agriculture.

The exemption criteria above do not apply to research involving prisoners. (Subpart C of 45 CFR 46).

In addition, the exemption criteria listed as #2 above, does not apply to research involving children (Subpart D of 45 CFR 46) except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.
Unless at least one of the following criteria are true, clinical investigations involving human participants are subject to IRB review under FDA regulations

Exempt research under the FDA regulations:

1) Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.

2) Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.

3) Emergency use of a test article (see definition in Chapter 3, Section B1), provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. See Chapter 9, Section "Emergency Use of a Drug or Device"

4) Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

When both DHHS and FDA regulations apply to research involving human subjects, the UI IRB applies the most restrictive regulations from each to the research being conducted to ensure the protections of the rights and welfare of the human participants.

B. Expedited Review

Federal regulations recognize certain kinds of research that may be reviewed by an IRB through an expedited review procedure [45 CFR 46.110 (DHHS) and 21 CFR 56.110 (FDA)]. Expedited review means that the IRB chairs (or his/her IRB member designee) are responsible for the review and approval. Expedited review does not mean that the review occurs quickly.

The IRB chair (or his/her IRB member designee) is the sole authority for determining whether the research meets the expedited criteria, based on review and approval of the investigator's application to the IRB. The chair (or his/her IRB member designee) retains the discretionary right to require full board review, even when the project appears to meet the criteria for expedited review. The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless the investigator has documented that reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

The expedited review process may be used for the initial review of projects involving a) no more than minimal risk, and b) only those procedures listed in one or more of the following categories. The activities listed are not deemed to be of minimal risk simply because they are included on the list. Inclusion on the list merely means that the activity is eligible for expedited
review when the specific circumstances of the proposed research involve no more than minimal risk to human subjects. If the research project as a whole involves more than minimal risk, it must be reviewed by the full board even if the activities are limited to those listed.

1) Research on drugs for which an investigational new drug application is not required or research on medical devices for which a) an investigational device exemption application is not required or b) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2) Collection of blood samples by finger stick, heel stick, ear stick or venipuncture as follows:
   (a) from healthy, nonpregnant adults, who weigh at least 110 pounds. For these subjects, amounts drawn may not exceed 550 ml in an 8 weeks period and no more than 2 times per week; OR
   (b) from other adults and children, considering age, weight, and health, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml/kg in an 8-week period and collection may not occur more frequently than 2 times per week.

3) Prospective collection of biological specimens for research purposes by noninvasive means. Examples:
   (a) hair and nail clippings, in a nondisfiguring manner;
   (b) deciduous teeth at the time of exfoliation or if routine patient care indicates a need for extraction;
   (c) permanent teeth if patient care indicates a need for extraction;
   (d) excreta and external secretions (including sweat);
   (e) uncanulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or applying a dilute citric solution to the tongue;
   (f) placenta removed at delivery;
   (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
   (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
   (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
   (j) sputum collected after saline mist nebulization.

4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples:
   (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;
   (b) weighing or testing sensory acuity;
   (c) magnetic resonance imaging;
   (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;
   (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight and health of the individual.
5) Research involving materials (data, documents, records or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

6) Collection of data from voice, video, digital or image recordings made for research purposes.

7) Research on individual or group characteristics or behavior (including but not limited to research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Modifications to previously approved research projects may be expedited if the modification involves only a minor modification to the approved project during the (one year or less) period of approval. See Chapter 7, Section A below for a definition of minor modification.

The continuing review of research may be reviewed using the expedited procedures in the following instances:

- If the project was previously reviewed and approved using the expedited procedure and conditions have not changed such that the research would no longer be eligible for expedited review (e.g. protocol change, or experience shows the research to be of greater than minimal risk).

- If continuing review of the research was previously approved by the convened IRB and conditions have changed to make the research eligible for expedited review under criteria 1 through 7 above (e.g. research is within those categories and experience confirms the research to be of no greater than minimal risk)

- If continuing review of the research was previously approved by the convened IRB and (a) the research is permanently closed to the enrollment of new subjects, and all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects; or (b) no subjects have been enrolled and no additional risks have been identified; or (c) the remaining research activities are limited to data analysis.

- If continuing review of the research was previously approved by the convened IRB and a) the research is not conducted under an investigational new drug application or an investigational device exemption, and b) the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk, and c) no additional risks have been identified since IRB review at a convened meeting.

The expedited review procedure is not used for the continuing review of research where the research involves more than minimal risk (except for when no subjects have been enrolled and no additional risks have been identified) or where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections are implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal (except for when no subjects have been enrolled and no additional risks have been identified). The expedited review procedure is not used for classified research.
No studies involving prisoners may be reviewed under expedited procedures regardless of whether or not they meet the criteria above EXCEPT for new studies limited in scope to retrospective review of prisoners’ records and minor modifications to already approved research. In the case of these exceptions, approval of the research can only be granted after review of and comment on the protocol by the prisoner advocate member of the IRB.

C. Full Board Review

Human subjects research that is not classified as exempt or expedited requires review by the full IRB at a convened meeting.

How often does the full board meet to review applications?
IRB-01 meets once or twice each week, and IRB-02 is scheduled to meet twice a month.

How much in advance should I submit my application if it requires full board review?
Due to the volume for IRB-01, and the bi-monthly meetings for IRB-02, investigators are advised to allow a minimum of three to four weeks for an application to be scheduled for review at a convened meeting.

A full board meeting may be canceled by the chair due to:
  a) insufficient number of applications requiring full board review,
  b) University holiday,
  c) inability to secure a quorum for attendance, or
  d) other reasons as may arise that make a scheduled meeting unnecessary or otherwise inappropriate.

How are projects reviewed by the full board?
The University of Iowa IRBs use a primary reviewer system for full board reviews. Application materials are normally sent to the IRB members scheduled to attend a meeting at least one week in advance of the meeting. All members attending the meeting receive the application itself, the Informed Consent Document, and other materials such as advertisements or recruitment letters. One member who is designated by the chair as the primary reviewer for a project, also receives the complete grant application or protocol, any sample consent documents (DHHS or other sponsor sample consent, if available) and for investigational drug/device studies, the Investigator’s Brochure. At the discretion of the chair and/or primary reviewer, the investigator may be invited to attend the meeting for the purpose of additional clarification or discussion. The investigator will be asked to leave the meeting for subsequent discussion and voting. The primary reviewer leads the discussion of each project at the full board meeting.

The board determines whether the project meets the criteria for approval or whether revisions to the study design are required. The Informed Consent Document is reviewed for accuracy, clarity, and inclusion of required and optional elements of consent. The primary reviewer makes a recommendation to the convened IRB to:
  1) approve as submitted;
  2) approve pending receipt and review of required minor revisions to study proceduresInformed Consent Document(s), or other written materials;
  3) table pending review at a subsequent full board meeting after receipt of significant additional information or revisions, or
  4) disapprove.

At the discretion of the chair, voting may be by written ballot or a show of hands. The members vote to abstain, agree or disagree with the recommendation and, by a majority of those
present at the meeting (when a quorum is constituted), the recommendation is either approved or disapproved.

Written minutes of each full board meeting include:
- which IRB (IRB-01 or IRB-02) reviewed the project,
- attendance (those recused or not present are named),
- actions taken by the board
- the number of votes to agree, disagree, and the number abstaining (without individual identification),
- protocol-specific regulatory determinations,
- justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample informed consent document (if there is one),
- Whenever a significant risk/non-significant risk determination is made, the rationale for the significant risk/non-significant risk device determination.
- the basis for requiring changes in or disapproving the research,
- the length of time until the next review (not to exceed one year),
- a summary of the discussion of controverted issues and their resolution,
- specific comments relevant to inclusion of certain populations in the research, and
- where appropriate, information regarding expedited approvals, modifications, terminations, emergency/single patient use, unanticipated problems involving risks to subjects or others, and any other business appropriate for board meetings.

D. Special Types of Approval – These only apply to specific, funded projects.

1. Overall Approval

Overall approval is limited to an IRB application for a training grant, center grant, or program project grant that involves human subjects. This type of approval allows the Principal Investigator and Sponsored Programs to provide a single IRB approval date to the funding agency for the overall award itself. Overall approval is therefore an administrative tool. It does not indicate approval for any of the specific projects described in the grant.

Human subjects may not be enrolled in any of the specific projects described in the grant under an overall approval alone. Overall approval is given via the expedited review procedure. To obtain approval for the individual projects described in the training grant, center grant, or program project grant, the principal investigator of each individual project should submit a New Project Application through HawkIRB for each project that involves human subjects.

When completing the application form for each individual project in HawkIRB, the investigator should indicate the funding source as the funding agency that provided the overall award.

2. Concept Approval

Concept approval is limited to an IRB application for a funded project where the funding agency has approved an initial period of time for development of the final protocol, questionnaires, data forms, or similar activities. Since the IRB may not approve "draft" protocols or Informed Consent Documents, concept approval shows that the IRB has approved the study in concept only, so that Sponsored Programs can award the funds for the preliminary work. Concept approval is therefore an administrative tool. It does not indicate approval for the enrollment of human subjects.

Human subjects may not be enrolled in a project given concept approval. Concept approval is given via the expedited review procedure. To obtain approval for enrolling human subjects, the investigator should submit a Modification/Update Form in HawkIRB for the study that received concept approval. In the Modification/Update Form, you should change Question IV.1 to indicate that you want the Regular review. This will open up additional questions for you to answer in order
to complete the application. An Informed Consent Document and any other materials, such as interview scripts or questionnaires, should be attached to the Modification/Update Form.
Chapter 5 -- The Informed Consent Process

A. The Process of Consent and Assent
   1. Consent & Assent

   Obtaining informed consent is a basic ethical obligation for researchers. The process of consent should ensure that potential subjects are provided with information about the research project that is understandable and permits the subject to make an informed and voluntary decision about whether or not to participate. The amount of information and the manner of presentation is generally related to the complexity and risk involved in the research study. While the initial process is prospective and takes place prior to any research activity, consent should also be an ongoing educational interaction between the investigator and the research subject that continues throughout the study.

   The informed consent process is not an exercise in persuasion. If an investigator has a relationship with potential subjects (physician-patient, instructor-student, employer-employee), care should be taken to avoid recruitment methods that may be seen as coercive due to the special relationship between parties.

   Except in certain minimal risk studies, the Informed Consent Document:
   - is typically signed after the investigator has verbally explained the purpose and procedures involved in the study, answered questions, and otherwise provided information that permits the subject to make a prospective, informed decision.
   - must be signed and dated before any study data collection procedures begin.
   - serves as a written source of information for the subject and documents the fact that the process of consent occurred.

   Consent is a legal concept. Only legally competent adults can give legally effective informed consent. Children and those individuals who are not competent to provide consent should be given the opportunity to assent to participate in the research project. Assent is a knowledgeable agreement to participate in the project. Adequate provisions should be made for soliciting the independent, non-coerced assent from children or cognitively impaired persons who are capable of a knowledgeable agreement. In general, the IRB recommends that children age seven and older, and most cognitively impaired adults, be given the opportunity to assent.

   If the person from whom assent is sought refuses, the person should not be enrolled, even if the parent or legally authorized representative gives permission. (The IRB may make an exception to this guideline in studies of children with life-threatening illnesses who are eligible for research treatment protocols.) Alternatively, if the person from whom assent is sought agrees to participate, the person may not be enrolled if the parent or legally authorized representative does not give permission. In rare circumstances, depending on the nature of the study and the age and circumstances of the child, the IRB may waive the requirement for parental or legally authorized representative permission.

   The subject must affirmatively agree to participate in a research study. The UI does not recognize a “passive” consent (i.e. the assumption of agreement to participation in the absence of any response). For example, sending a letter home to parents telling them that the research is taking place in a school and giving them the opportunity to object if they do not want their child to participate is NOT recognized as a valid consent process by the UI IRBs.
In cases where assent is obtained from a child or cognitively impaired subject, permission must also be obtained from a legally authorized representative. [NOTE: See Chapter 8, Section D, Vulnerable Populations, for more information about enrolling cognitively impaired subjects in research studies.]

A child by DHHS definition is a person who has not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. By FDA definition, a child is a person who has not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted. For purposes of research conducted in the state of Iowa, the term “child” as used in both the DHHS and FDA definitions is analogous to “minor” under Iowa Code and is viewed as “an unmarried person under the age of eighteen years.” (Iowa Code 600A.2(12))

In cases of human subjects research under the authority of the UI IRB(s) but conducted outside of the state of Iowa, the UI IRB confers with the UI Office of General Counsel regarding the applicability of other state, national, or international laws to the particular project. These cases are identified in the pre-review process of an application to the IRB and the advice of counsel is sought prior to the approval of the study. In general, the UI IRB will apply the law of the state in which the research is being conducted. For example, if a project involves children and one of the recruitment sites is in a bordering state, the laws of the bordering state will be evaluated to which individuals meet the DHHS and FDA definition of “children” at that site.

2. Legally Authorized Representative
In studies involving children in the state of Iowa, the legally authorized representative is:

- the parent, OR
- the court-appointed guardian

A legal guardian in the state of Iowa is defined as a person who is not the parent of a child, but who has been appointed by a court or juvenile court having jurisdiction over the child, to have a permanent self-sustaining relationship with the child and to make important decisions which have a permanent effect on the life and development of that child and to promote the general welfare of that child. A guardian may be a court or a juvenile court.

Unless otherwise enlarged or circumscribed by a court or juvenile court having jurisdiction over the child or by operation of law, the rights and duties of a guardian with respect to a child shall be as follows:

a. To consent to marriage, enlistment in the armed forces of the United States, or medical, psychiatric, or surgical treatment.

b. To serve as a guardian ad litem, unless the interests of the guardian conflict with the interests of the child or unless another person has been appointed guardian ad litem.

c. To serve as custodian, unless another person has been appointed custodian.

d. To make periodic visitations if the guardian does not have physical possession or custody of the child.

e. To consent to adoption and to make any other decision that the parents could have made when the parent-child relationship existed.

f. To make other decisions involving protection, education, and care and control of the child.
In studies conducted in the state of Iowa involving cognitively impaired adults, the legally authorized representative is:

- the designated proxy (such as a Durable Power of Attorney for Health Care)
- court-appointed guardian
- spouse [This does NOT include “common law” spouses]
- adult child
- parent
- adult sibling.

In studies involving cognitively impaired adults, permission must be sought from the first existing person in the above list, even if another relative is more conveniently available.

Examples:

- If a married person does not have a designated proxy or court-appointed guardian, the investigator must obtain permission from the spouse, even if an adult child or parent is present and available.
- If a divorced person has adult children and does not have a designated proxy or court-appointed guardian, then the investigator must obtain permission from an adult child, even if a parent is present and available.
- If the potential subject is unconscious but there is an individual who claims to be the “common-law” spouse of the subject, unless you have documentation that the person is the designated proxy or court-appointed guardian of the potential subject, then you would have to obtain the permission of the next eligible LAR (i.e. adult child, parent, adult sibling).
- If the potential subject is being recruited from a site that is not in the state of Iowa (but the project is under the oversight of the UI IRB), laws governing the other site defining the legal ability of a person to consent on behalf of a subject to the subject’s participation in the procedures being conducted as part of the research will define the legally authorized representative of the subject being recruited at that site.

B. Standard Informed Consent Document

The purpose of an Informed Consent Document is to provide subjects with a written source of information for future reference and to document the fact that the process of informed consent occurred prior to the subject's participation. The form generally serves as a basis for the initial presentation of the study to the potential subject. Typically, informed consent is documented by using the written Informed Consent Document approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. The subject or the representative must always be provided adequate opportunity to read the consent document, consider their participation, and ask questions before the consent document is signed. A copy of the Informed Consent Document should be given to the subject. Unless the investigator has requested and been granted a waiver of documentation of consent, the subject's signature on an Informed Consent Document is required prior to beginning any study procedures.

Although the research study and Consent Document must be reviewed and approved by the IRB at least once per year, subjects enrolled in the study generally sign the Informed Consent Document only once, when initially enrolled. The exception to this is when the IRB or study sponsor requires subjects to sign a revised Consent Document due to a modification in the protocol or adding new information that may affect the subject's willingness to participate further in the study. This illustrates one example of how the consent process is an ongoing interaction between the investigator and the research subject.
Consent Template and HawkIRB

The Informed Consent Document template is available via HawkIRB and contains examples of text for preparing an Informed Consent Document. At the end of the template, there is an Appendix containing suggested language for special situations. By following the template, the investigator ensures that the basic and additional elements of consent as required by the federal regulations are included.

For all New Project applications, you must begin with the consent template that is available at the end of the HawkIRB application. In HawkIRB, the consent document is populated with template language based on your responses to various questions within the application. Thus, when you download the consent form from HawkIRB for editing prior to final submission, many of the pertinent sections of the consent template are already included.

The IRB expects all persons involved in the informed consent process to be individually listed, along with degrees, as members of the research team at the beginning of the Informed Consent Document.

Basic Elements of Informed Consent

The basic elements of informed consent, as described in 45 CFR 46.116 (DHHS) and 21 CFR 50.25 (FDA), are as follows:

- A statement that the study involves research, an explanation of the purposes of the research and 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 to the subject.
- A description of any benefits to the subject or to others which may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. For studies regulated by the FDA, note the possibility that the Food and Drug Administration may inspect the records. \[21 CFR 50.25(a)(5)\]
- For research involving more than minimal risk, an explanation as to whether any compensation 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.
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Additional Elements of Informed Consent

The federal regulations stipulate that additional elements of informed consent should be provided when appropriate. The additional elements include:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

Any additional costs to the subject that may result from participation in the research.

The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

The approximate number of subjects involved in the study.

Common Problems with the Written Informed Consent Document

Some common problems with the Informed Consent Document include the use of jargon, technical, or scientific terms that a lay person would not understand, and units of measure given in metric rather than the lay equivalents. Ordinary language should replace technical terms (e.g., upper extremities are better referred to as arms, hematoma as a bruise, venipuncture as taking blood from your arm with a needle, and so forth.) A website that is helpful for converting medical terminology to lay language can be found by clicking on the following link, Medical Terminology in Lay Language.

But perhaps the most common problem with Informed Consent Documents is that they are written at a reading level several grades higher than the average subject would understand. Informed Consent Documents should be written at a reading level that potential subjects would understand. For most projects, an eighth grade reading level is suggested. Most word processing programs can determine a document's reading level.

Tips for writing a "user-friendly" Informed Consent Document:

- Write the Consent as though you were speaking to the person who will read it, using “you” and “your,” “we” and “our,” rather than third person.
- Use language that could be understood by a junior high student.
- Put technical jargon into lay terms (e.g., describe the amount of a blood draw in teaspoons rather than milliliters; use “cancer” rather than “carcinoma”).
- Clearly define complicated terms (e.g., randomization means the study treatment you’ll receive will be decided by chance, like flipping a coin).
- Don’t give a lot of technical information that participants don’t need to know (e.g., complicated methods of determining drug doses, exhaustive lists of specific lab tests).
- Use bulleted lists rather than long sentences.
- Use headings and subheadings as appropriate with logical and consistent formatting.
- Use tables and charts to explain when/where each procedure will take place.
- Use pictures and diagrams to help describe devices.
- Number each page of the document.
- Use hard page breaks to eliminate “widow” and “orphan” lines of text.
- Use a font with a serif (e.g., Times New Roman – easier to read).
- Use consistent and reasonable font size (e.g., 12 point).
- Do not “right justify” the text.

Teenage Subjects and How to Handle Wording on the Consent Document

If you plan to recruit teenage subjects (in this instance, teenage means a child older than 12 but less than 18 years of age), and the Informed Consent Document is written at an appropriate reading level, both the teenager and the parent/guardian may sign the Informed Consent. The teenager’s signature on the Informed Consent Document indicates knowledgeable agreement to participate (assent), and the parent/guardian’s signature indicates legal consent.
In this situation, rather than using “you/your child,” use the word “you” throughout, and insert the following statements at the very beginning of the Consent:

- If you are the parent/guardian of a child who is being invited to be in this study, the word “you” in this document refers to your child. You will be asked to read and sign this document to give permission for your child to participate.
- If you are a teenager reading this document because you are being invited to be in this study, the word “you” in this document refers to you. You will be asked to read and sign this document to indicate your willingness to participate.

Signature Lines
In general, the Informed Consent Document must include signature lines for:

1. the subject AND [See Exception #1]
2. the person who obtained consent AND [See Exception #2]
3. for studies involving children, a parent or legal guardian; for studies involving cognitively impaired individuals, a legally authorized representative.

Exceptions:
1. In some types of studies (e.g., mail-out surveys), the investigator may request a waiver of the subject’s signature (see waiver of documentation of consent in Chapter 5 below) when submitting the New Project Application. In such cases, the conclusion of the Informed Consent Document (which could be formatted as a letter to the subject) should inform the subject that returning the survey will be considered evidence of consent.

   Note: the HIPAA Privacy Rule does not permit a waiver of documentation of authorization if the study data include protected health information. Thus, studies which utilize mailed surveys and wish to also obtain HIPAA authorization to access medical record information must include a process for obtaining a signed combined consent and HIPAA authorization.

2. When there is no verbal communication with potential subjects (e.g., mail-out surveys), the signature of the person who obtained consent may also be deleted.

NOTE: An auditor/witness signature line is needed only if specifically required by the IRB or the funding agency/company. However, if this line is included on the consent, the consent must always be witnessed and this line signed.

C. Special Consenting Circumstances & Documents
1. VAMC Consent Process
   The Veterans Affairs Medical Center requires that the standard Informed Consent Document be copied onto its own special form. The instructions for its use are on the Forms page of the Human Subjects Office website and the form is a template choice on the Consent/Assent attachments page of HawkIRB.

   If your project involves the VAMC and tissue/sample storage for future use, you should check with the VAMC Research Office (158-7645) to determine if this is allowable PRIOR to adding the other site to the tissue storage section of the consent document. Include a written statement from the VAMC research office acknowledging permission to store tissue/samples for future use as an attachment to the HawkIRB application.

2. Record of Consent or UIHC Consent Process
When a research project involves University of Iowa Health Care (UIHC) patients, it is UIHC policy that a signed copy of the standard Informed Consent Document must be placed in the subject’s medical record chart. However, there are circumstances when the investigator may wish to place a more confidential document in the patient’s medical record. In such cases, a Record of Consent may be used and may be required by the IRB. The Record of Consent does not contain the project title or a description of the study. The only identifying information is the IRB ID number.

Using a Record of Consent form means that the subject would sign two research Consent forms. First, the subject would sign the regular Informed Consent Document, and the investigator would keep that copy in his/her research records. The subject would also sign the Record of Consent, and the investigator would place that form in the subject’s medical record chart.

A Record of Consent may be used (in addition to the regular Informed Consent Document) when:

- additional confidentiality is desired (e.g., genetic studies, studies of illicit drug use or illegal behaviors, some psychiatric research), OR
- the information contained in the regular Informed Consent Document is not relevant to the subject’s care (e.g., single blood draw for a lab study).

The investigator may propose using this form when submitting an application to the IRB. For certain studies, the IRB might require the use of a Record of Consent as a condition of approval.

A template Record of Consent is available as a choice on the Consent/Assent attachments page of HawkIRB.

3. Assent Process

An Assent Document is used when the investigator recruits subjects who, by age or circumstance, are not able to give legally effective informed consent. When legally effective informed consent cannot be obtained, the investigator should obtain the "assent" of the child or cognitively impaired subject. This form documents the child’s or cognitively impaired subject's knowledgeable agreement, or assent, to participate in a research project. The investigator should respect the decision of a child or cognitively impaired subject not to participate, even when the parent or legally authorized representative gives permission, unless specifically instructed otherwise by the IRB.

For studies involving children, the IRB may recommend that this form be used with children who are in the 7-12 age range, but it may also be used when teenagers (as defined in Chapter 5, Section B above) are being recruited to enhance their comprehension if the study involves complicated procedures.

When using an Assent form, the child or cognitively impaired adult should sign the Assent to indicate knowledgeable agreement (assent) to participate. In addition, the parent/guardian or legally authorized representative should sign the full Informed Consent Document to document his/her permission for the child or cognitively impaired adult to participate.

A template Assent Document is available as a choice on the Consent/Assent attachments page of HawkIRB.

4. Non-English Speaking Subjects & Consent

When an investigator anticipates enrolling non-English-speaking subjects, the protocol must reflect the methods for assuring full understanding, possibly with the assistance of an interpreter or
by using translated Informed Consent Document(s). If the investigator intends to use a translated version of the Informed Consent Document(s), the IRB must review and approve the translated version(s) prior to use. The credentials of the person who did the translation must be provided to the IRB.

If a non-English speaking subject is unexpectedly encountered, investigators will not have a written translation of the consent document and must rely on oral translation. Investigators should carefully consider the ethical/legal ramifications of enrolling subjects when a language barrier exists. If the subject does not clearly understand the information presented, the subject's consent will not truly be informed and may not be legally effective.

If investigators enroll subjects without an IRB approved written translation, they must translate the IRB approved "short form" written consent document (available on our website), into a language the subject understands and submit it to the IRB for approval prior to its use. This translated form documents that the elements of informed consent were presented orally. The short form states that the elements of informed consent required by the regulations have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there must be a witness to the oral presentation. Also, the IRB must approve a written summary of what is to be said to the subject (if the standard Informed Consent Document is presented orally, this requirement has been met). Only the short form itself must be signed and dated by the subject or the representative. However, the witness must sign and date both the short form and a copy of the full Informed Consent Document, and the investigator who obtains consent must sign and date the full Informed Consent Document. A copy of the full Informed Consent Document must be given to the subject or the representative in addition to a copy of the short form.

The IRB has approved a "short form" consent document for Spanish-speaking subjects. This is available as a choice on the Consent/Assent attachments page of HawkIRB.

5. Waivers & Consent

Waiver of Documentation of Consent

In some situations, the IRB may waive the requirement for obtaining a signed Informed Consent Document. The DHHS regulations (45 CFR 46.117(c)) state that a signed consent form may be waived if the IRB determines that:

- the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality;

  Example 1: Some types of studies that fall into this category are survey or interview studies that contain highly sensitive (e.g., criminal behavior, sexual behavior) questions.

OR

- the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

  Example 2: Studies that may meet this criteria include mail out surveys about topics that could not reasonably damage a participant's reputation or employability or be otherwise stigmatizing.

The FDA regulations (21 CFR 56.109(c)) state that a signed consent form may be waived if the IRB determines that:
• the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; OR

• the requirements in 21 CFR 50.24 for an exception from informed consent for emergency research are met.

Waiver of documentation of consent may mean that no written document is provided to the subject at all:

Example 3: Random-dial telephone survey study. In this type of study, the telephone interview would begin with a script that includes all of the required elements of consent, but the study subjects would receive no written information about the study, either before or after the interview. The telephone script containing the elements of consent must be included in the New Project Application to be reviewed and approved by the IRB.

The waiver of documentation of consent may also mean only that the subject's signature does not have to be obtained. The regulations stipulate that the IRB may still require that the investigator provide the subject with a written statement about the research when granting a waiver of documentation.

Example 4: In a mailed-out survey study, the IRB may determine that it is reasonable for the investigator to provide the subjects with a cover letter containing all of the basic elements of consent. The letter would simply conclude with a statement that returning the survey or questionnaire would be considered agreement to participate.

A template of an Informed Consent as a Letter to the Subject is available as a choice on the Consent/Assent attachments page of HawkIRB.

Waiver of Elements of Consent (Not available under FDA regulations)

Some research projects would not be possible if informed consent from participants were required. The IRB may consider waiving the requirement for some or all of the elements of informed consent (45 CFR 46.116(d)) only if the study is not under the authority of the FDA. The regulations state that informed consent may be waived in full or in part if the IRB determines that:

• the research involves no more than minimal risk to the subjects; AND

• the waiver or alteration will not adversely affect the rights and welfare of the subjects; AND

• the research could not practicably be carried out without the waiver or alteration; AND

• whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Example 1: Studies in which all of the elements of consent have been waived. These may be retrospective chart review studies, or studies of existing pathology specimens (all specimens to be studied have already been collected and are "on the shelf" at the time of the IRB application).

In the types of situations given in the preceding example, presuming that the study can be classified as minimal risk and that adequate provisions for protecting the confidentiality of the data are in place, the IRB chairs generally find that obtaining consent is impracticable (not possible).

There are certain types of studies in which some of the elements of consent can be waived. These include, but are not limited to, certain types of ethnographic research, and studies that require deception.
Example 2: In a minimal risk study involving playing a computer game to test subjects’ responses to differential pay-offs or reinforcements, the investigator might indicate in the Informed Consent Document that the purpose of the study is to test reaction time. This deception may be necessary because the study would be compromised if subjects were told the true purpose. In this scenario, one of the basic elements of consent -- the purpose of the study -- could be waived by the IRB chair, and not included in the Informed Consent Document.

If the investigator seeks a waiver of any or all of the elements of consent, the New Project Application should describe the reasons for the request, paying particular attention to why the research project would be “impracticable.” The term "impracticable" means more than simple inconvenience - it means that the research could not be conducted without the waiver.

Exception from Informed Consent and Waiver of Informed Consent Requirements in Certain Emergency Research

Both the FDA regulations and the DHHS regulations allow for some types of emergency research to be conducted without prior consent of the subject or their legally authorized representative. The FDA “exception from Informed Consent” regulations are found at 21 CFR 50.24. On October 2, 1996, the Secretary of DHHS announced under 45 CFR 46.101(i), a waiver of the applicability of the 45 CFR 46 requirement for obtaining and documenting informed consent for a strictly limited class of research, involving research activities that may be carried out in human subjects who are in need of emergency therapy and for whom, because of the subjects’ medical condition and the unavailability of legally authorized representatives of the subjects, no legally effective informed consent can be obtained. See the Special Topics section on Emergency Research for additional information.

D. Privacy and Confidentiality

An issue of primary importance is the protection of both the privacy of research subjects and maintaining the confidentiality of data. Federal regulations [45 CFR 46.111(a)(7) (DHHS) and 21 CFR 56.111(a)(7) (FDA)] require that the IRB only approve research where there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. Although related, the concepts of privacy and confidentiality are distinct from one another. Confidentiality means the ethical or legal right that information is considered private and will be held secret unless consent is provided permitting disclosure.

Privacy is the freedom from unauthorized intrusion or the state of being let alone and able to keep certain personal information to oneself. By its nature, research may invade the privacy of individual subjects in that it may require the collection, use, or access to identifiable information that would otherwise not be shared with others. When this is required for the purposes of the research, the private information involved should be the minimum necessary to accomplish the goals of the research.

The investigator must have sound plans to protect the subject's identity, must collect only the necessary identified information to conduct the study, and must have procedures in place to maintain the confidentiality of the research records. Care should be taken to explain the mechanisms that have been devised, for example, the use of numbering or code systems or safely locked files in private offices. Furthermore, the investigator should describe who has access to the data and under what circumstances a code system may be broken. Without appropriate safeguards, problems may arise from long-term retention of records.

Special Circumstances for Added Protections:
1. Video/Audio tapes and/or Photographs. A special situation arises for video or taped data
and photographs since these media provide additional potential means for subject
identification. Investigators must secure subject consent after explicitly mentioning these
practices. They should also explain plans for final disposition or destruction of such
records.

2. HIPAA. If a research study involves protected health information and involves consent
from subjects, the consent document signed by the subject must contain a section entitled
“Will My Health Information be Used During this Study?” This section of the consent serves
as “authorization” from the subject for researchers to access or create health information
about the subject. For more information about HIPAA and protected health information,
click on the link on the title of this paragraph.

**NIH Certificate of Confidentiality** and other Safeguards to prevent potential criminal prosecution of
the participating human subject.

(from NIH Office of External Research web site)

**What is an NIH Certificate of Confidentiality?**

Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect
the privacy of research subjects by protecting investigators and institutions from being compelled
to release information that could be used to identify subjects with a research project. Certificates
of Confidentiality are issued to institutions or universities where the research is conducted. They
allow the investigator and others who have access to research records to refuse to disclose
identifying information in any civil, criminal, administrative, legislative, or other proceedings,
whether at the federal, state, or local level.

Identifying information in this context is broadly defined as any item or combination of items
in the research data that could lead directly or indirectly to the identification of a research subject.
By protecting researchers and institutions from being compelled to disclose information that would
identify research participants, Certificates of Confidentiality help achieve the research objectives
and promote participation in studies by assuring privacy to subjects.

**For what types of research might I obtain a Certificate of Confidentiality?**

Certificates can be used for biomedical, behavioral, clinical or other types of research that is
sensitive. Sensitive means that disclosure of identifying information could have adverse
consequences for subjects or damage their financial standing, employability, insurability, or
reputation.

Examples of sensitive research activities include but are not limited to the following:

- Collecting genetic information;
- Collecting information on psychological well-being of subjects;
- Collecting information on subjects' sexual attitudes, preferences or practices;
- Collecting data on substance abuse or other illegal risk behaviors;
- Studies where subjects may be involved in litigation related to exposures under study (e.g.,
  breast implants, environmental or occupational exposures).

**How long is the protection afforded by the Certificate in effect?**

A Certificate of Confidentiality protects personally identifiable information about subjects in the
research project while the Certificate is in effect. Generally, Certificates are effective on the date
of issuance or upon commencement of the research project if that occurs after the date of
issuance. The expiration date should correspond to the completion of the study. The Certificate
will state the date upon which it becomes effective and the date upon which it expires. A
Certificate of Confidentiality protects all information identifiable to any individual who participates
as a research subject (i.e., about whom the investigator maintains identifying information) during
any time the Certificate is in effect. An extension of coverage must be requested if the research extends beyond the expiration date of the original Certificate. However, the protection afforded by the Certificate is permanent. All personally identifiable information maintained about participants in the project while the Certificate is in effect is protected in perpetuity.

Are there circumstances when I am allowed to disclose subject research information?
While Certificates protect against involuntary disclosure, investigators should note that research subjects might voluntarily disclose their research data or information. Subjects may disclose information to physicians or other third parties. They may also authorize in writing the investigator to release the information to insurers, employers, or other third parties. In such cases, researchers may not use the Certificate to refuse disclosure. Moreover, researchers are not prevented from the voluntary disclosure of matters such as child abuse, reportable communicable diseases, or subject's threatened violence to self or others. However, if the researcher intends to make any voluntary disclosures, the consent form must specify such disclosure.

How do I let subjects know that a Certificate of Confidentiality is in effect for the study?
In the Informed Consent Document, investigators should tell research subjects that a Certificate is in effect. Subjects should be given a fair and clear explanation of the protection that it affords, including the limitations and exceptions noted above. The University of Iowa Informed Consent Document template contains suggested language to describe the protection afforded by a Certificate of Confidentiality.

How do I apply for and obtain a Certificate of Confidentiality?
The investigator may choose to apply for a Certificate of Confidentiality on his or her own, or the IRB may require that an investigator obtain a Certificate prior to conducting the research. Investigators who intend to apply for a Certificate of Confidentiality should contact the Human Subjects Office regarding procedural steps for IRB approval and communicating with NIH. Complete information regarding the NIH Certificate of Confidentiality is available on the NIH Office of Extramural Research web site.

What are the procedures at the UI?
Because NIH requires that the investigator submit an IRB-approved Consent Document that includes a description of the Certificate of Confidentiality, the investigator must wait until after receiving IRB approval before applying for the Certificate. This means that the investigator will have in hand a stamped, approved Informed Consent Document that describes the special protections of a Certificate, but will not yet have the Certificate itself. Therefore, in order to ensure that the Consent is not used before obtaining the Certificate, the HSO places a "watermark" across each page of the stamped Consent that indicates it may not to be used to enroll human subjects.

The PI should apply for a Certificate following the instructions on the NIH web site (http://grants.nih.gov/grants/policy/coc/appl_extramural.htm). The application letter must be signed by a University of Iowa institutional official so the PI should bring the application letter to the Human Subjects Office and the HSO will obtain the institutional official's signature and return the signed letter to the PI.

UI Procedures Summarized:
1. Submit research project application to the HSO. Include an Informed Consent Document with the Certificate of Confidentiality Language inserted.
2. After project approval by the IRB, you will receive an IRB stamped, approved consent document with a "watermark" across each page. YOU MAY NOT USE THIS CONSENT DOCUMENT TO ENROLL SUBJECTS AT THIS TIME.

3. Apply for the Certificate following the instructions of the NIH web site (http://grants.nih.gov/grants/policy/coc/appl_extramural.htm). This involves crafting an application letter to the NIH.

4. After finalizing the application letter, bring it to the Human Subjects Office. HSO staff will obtain the UI institutional official’s signature and will return the signed letter to you.

5. Send application to NIH and await Certificate.

6. When you receive the Certificate from the NIH, you will need to submit a modification application via HawkIRB. Attach a copy of the certificate.

7. The IRB chair will review the application and upon approval the “watermark” will be removed from the approved consent document and it will be released to the PI through HawkIRB.

Note: If the IRB requires you to obtain a Certificate of Confidentiality as a condition of approval, you will need to revise your consent document and send it back to our office for the "watermark."

E. Recruitment and Subject Compensation Issues

1. Recruitment

Recruitment strategies in any form must be reviewed by the IRB PRIOR to their implementation. There are some recruitment strategies that are either not allowed or allowed in very limited circumstances at the UI. They include the use of finder’s fees or recruitment incentives and the use of “cold calling” potential research subjects.

Finders Fees/Recruitment Incentives:

UI policy strictly prohibits the acceptance or use of finders fees, recruitment incentives, or bonuses of any type to enroll study subjects. A finder’s fee or recruitment incentive may include bonuses given by sponsors to investigators or research team members (coordinators) to boost enrollment or referral fees given to physicians for referring his/her patients to another investigator’s study. Payments to investigators, research team members, or subjects for recruitment that are provided to the individual outside of the UI system are NOT allowed.

Cold Calling:

UI policy generally restricts the use of “cold calls” to recruit subjects to research studies. An introductory letter or other informational material must first be sent or given directly to subjects prior to telephone contact. Exceptions may be made on a case-by-case basis, for example, if the potential subjects have previously agreed to be listed on a research registry for future research studies, are currently participating in a study conducted by the same investigator, or are frequently seen by or are well known to the investigator.

Acceptable strategies for recruitment of subjects for research can be varied and may include:

- Advertising to promote the study
- Direct communication with identified groups (patients, students, personnel)
- Referrals from other sources such as other physicians or disease registries

Advertising Materials

Recruitment materials, including brochures, flyers, advertisements, audio tapes, video tapes, and letters to potential subjects, must not contain coercive language or incentives. The information in recruitment materials should be an accurate presentation of the research study purpose and/or procedures.
Example 1: You have a study that involves comparing an investigational drug to a placebo. The advertisement for this study should therefore not mention the study drug only. Rather, it should indicate that some subjects in the study will receive a placebo, or describe the purpose of the study as comparing the investigational drug to a placebo.

Any material aimed at recruiting potential subjects into a study (including the final copy of the printed advertisement, audio or video tapes or websites) must be reviewed and approved by the IRB prior to being used. Suggested guidelines for an advertisement or recruitment letter or webpage appear below:

- Include the purpose of the project and/or briefly state what is expected of the subject.
- Include the time commitment required of the subject.
- Include the investigator's University department affiliation and where the research will take place.
- List a contact name and phone number.
- Do not include the name of commercial sponsors or products.
- Avoid phrases such as "help needed" or "subjects wanted." The recommended wording is "you are invited" or "participants invited."
- If participants will be paid for their time/effort, it is recommended that the wording "You will be paid for your time and effort" be used, rather than specifying a specific amount. Compensation should not be excessive to the nature of the project. Also, do not emphasize (for example, in large or bold type) the payment or the amount to be paid.
- Do not state or imply a certainty of a favorable outcome or other benefits beyond what is outlined in the consent document and protocol.
- Do not make claims that the drug, biologic or device is safe or effective for the purposes under investigation.
- Do not make claims that the drug, biologic or device is known to be equal or superior to any other drug, biologic, or device.
- Do not use terms such as "new treatment," "new medication," or "new drug" without explaining that it is investigational.
- Do not promise "free medical treatment," when the intent is only to say subjects will not be charged for taking part in the investigation.

Example 2: A Sample advertisement acceptable to the IRB:
ALLERGY STUDY: Interested persons are invited to participate in an allergy study being conducted by Dr. Mary Brown at the University of Iowa, Department of Internal Medicine. Study involves 6 visits over 3 months, and having blood drawn. Compensation available. If you are at least 18, have seasonal allergies, and would like more information, contact Sam Smith at 335-1111.

Use of UI staff, students or faculty as research subjects
UI Students as Research Subjects
Consistent with an overall concern that no research subject should be coerced, researchers should take particular precautions to avoid the unintentional or subliminal coercion that may occur when a potential research subject is also a student. For this reason, researchers should avoid using their own students as research subjects. Researchers who wish to use their own students should be able to provide a good scientific reason, rather than convenience, for selecting those students as research subjects. The research project should be relevant to the topic of the class, and participation should be part of the learning experience for the students.
In instances where investigators can provide a good reason for using their own students in their research, the IRB generally requires that someone other than the investigator (instructor) obtain informed consent and collect the data. When this is not possible, the IRB will consider other methods for obtaining consent and collecting data that would not reveal to the instructor whether or not a student participated in the research project until after final grades have been determined. The students should be informed of what these procedures are in the Informed Consent Document. Below are a few situations specific to the recruitment of students for research projects.

Extra Credit
The IRB may approve projects that give extra credit to students who participate in a research project only when alternative means of obtaining equivalent extra credit with equivalent effort is made available to students who do not wish to volunteer as research subjects. The IRB carefully reviews the alternatives to ensure that students are not being coerced into participating. For example, if volunteering for a survey project takes 30 minutes and the student's output is not evaluated for its quality to determine whether extra credit is given, the alternative should involve 30 minutes of effort and the output should not be evaluated (beyond assurance that a good faith effort was made).

The Informed Consent Document should make clear the consequences of withdrawing from a project prior to completion (e.g., will extra credit be given despite withdrawal?). As a general matter, the IRB favors giving credit even if the subject withdraws, unless the student withdraws immediately or there is clear evidence of bad faith on the part of the student.

Faculty Use of Class Assignments as Research Data
There may be circumstances when an investigator wishes to use required class assignments (e.g., journal entries in a communications study course) in his or her research. The course syllabus should clearly state that the assignments are required for the course, but that at the end of the semester, the instructor will ask the student to give permission to use the assignments for research purposes. It should be clear that participation will not affect a student's grade. The syllabus should describe the procedure to be used to ensure that the instructor does not know who has consented until after final grades have been determined (e.g., Informed Consent Document could be included with ACE forms and kept in a secretary's office until after grades have been determined).

Departmental Subject Pools
Some departments or colleges employ "subject pools" where students enrolled in introductory courses are recruited by investigators from both within and outside of the department for participation in research projects. Departments or colleges may impose their own standards for the type of research that may be conducted in this setting, and for who may have access to such subjects. Investigators who recruit from "subject pools" are still required to submit their projects to the IRB for review and approval. Beyond the considerations outlined above, academic units may impose their own additional constraints on using students as research subjects.

UI staff or Research Team members as Research Subjects
The recruitment of UI staff as research subjects should be undertaken with caution. It is important that supervisors in research settings refrain from recruiting or enrolling their own employees and staff to participate in their research. There can be inherent coercion in these situations and so should be avoided. However, the recruitment of UI staff who are unaffiliated with the research is acceptable.

Referrals from other sources
Referrals from other sources can include the sending of information about ongoing research to other local sources asking that they either pass the information on to potential subjects, or obtain written permission to refer the subject to the study investigator. It can also include distributing study information to appropriate advocacy groups or student groups perhaps by giving lectures or presentations to these groups. As stated previously, this type of recruitment strategy would require review and approval by the IRB prior to implementation but is otherwise not discouraged as long as you follow the strategies as outlined in the “Advertising Materials” section above.

2. Subject Compensation

Payment for participation in research may not be offered to the subject as a means of coercive persuasion. Rather, it should be a form of recognition for the investment of the subject's time, loss of wages, or other inconvenience incurred. Payments should be based on the research subject’s time and/or reimbursement for reasonable expenses incurred during his/her participation in the research study. This could include payment for parking, lodging or transportation. Payment should not be excessive to the nature of the project. Information on the UI procedure for how to process payment for research subjects can be found on The University of Iowa Accounting Services website: http://www.uiowa.edu/~fusas/.

Accordingly, compensation may not be withheld contingent on the subject's completion of the study. In most cases involving continued participation, compensation should be given on a reasonable prorated basis to avoid the impression that the investigator is coercing the subject to continue in a study or is punishing the subject for non-compliance. If compensation is pro-rated when a subject withdraws prior to completing the study, explain in your consent process how it is pro-rated.

In research advertisements, if participants will be paid for their time/effort, wording such as "You will be paid for your time and effort" should be used, rather than specifying a specific amount. Also, do not emphasize (for example, in large or bold type) the payment or the amount to be paid.
Chapter 6 -- New Project Applications and IRB Review and Approval.

Investigators are required to submit an application for IRB review PRIOR to initiating a research project. In September 2004, the Human Subjects Office began requiring all new project applications be submitted using a new electronic database system, HawkIRB. HawkIRB is an online application submission tool that uses “smart form” technology to guide investigators through the application process. Instructions for completing the new project application are contained within each section of the HawkIRB system. Many training sessions are held when new aspects of the system are introduced. HSO staff are available for consultation and help using the system. Please refer to the list on our HawkIRB FAQ page.

A. Signatures

The principal investigator must sign the final page of the HawkIRB new project application. This page must be printed following completion of the New Project application in HawkIRB. The HSO must receive the completed signature form for a new project before final approval can be given to the project. This signed page should be sent to the Human Subjects Office, 340 CMAB. This page assures that the PI is in compliance with all federal, state, and University policies as they apply to the study. In signing the final page of the application form, the investigator assures that:

- s/he is ultimately responsible for the conduct of the study.
- s/he agrees to comply with all applicable UI policies and procedures, and applicable federal, state and local laws.
- the application is consistent with proposal(s) submitted to external funding agencies.
- the research will only be performed by qualified personnel.
- all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions.
- s/he will not implement any changes in the approved IRB application, study protocol, or informed consent process without prior IRB approval (except in an emergency, if necessary to safeguard the well-being of a human participant).
- If unavailable to conduct this research personally, as when on sabbatical leave, s/he will arrange for another investigator to assume direct responsibility for the study. Either this person is named as another investigator in this application, or s/he will notify the IRB of such arrangements.
- s/he will obtain Continuing Review approval prior to 12:01 a.m on the date the approval for the study expires. S/he understands if s/he fails to apply for continuing review, approval for the study will automatically expire, and all study activity must cease until IRB approval is granted.
- If protected health information is used or created as part of this research project, the research team agrees NOT to reuse or disclose the information to any other person or entity (beyond the named research team) except as required by law, for authorized oversight of the research project, or unless subsequent IRB approval is obtained for such reuse or disclosure.
- If members of the research team access protected health information from a covered component in order to seek consent/authorization for research, such access is necessary for the research, is solely for that purpose, and the information will not be removed from the covered component.
- Neither the principal investigator nor any member of the research team have entered into a financial arrangement with a sponsor of this study whereby the value of the compensation to the principal investigator or any member of the research team for conducting the study could be influenced by the outcome of the study.
• s/he further assures that the proposed research is not currently being conducted and will not begin until IRB approval has been obtained.

The investigator is expected to be familiar with the policies contained in the University of Iowa Federalwide Assurance.

The signature of the departmental executive officer (department chair) also is required on the signature page of the New Project Application. If the departmental executive officer is the principal investigator, s/he may sign as both the investigator and the DEO. This signature of the DEO is an assurance that the PI:

• Is qualified to conduct the research as described in the application.
• Has adequate resources, facilities, and numbers of qualified staff to conduct the research as described in this application.
• Has used sound study design consistent with the standards of the investigator’s area of research.
• Has available time to oversee and conduct the project.

A student researcher may be listed as the principal investigator on the application forms, but a faculty or staff member must be a member of the research team and sign the application as the supervisor. The faculty signature assures that:

• s/he will meet with the student investigator on a regular basis and monitor study progress.
• The student is knowledgeable about the regulations and policies governing research with human subjects and has sufficient training and experience to conduct this particular study in accord with the approved protocol.
• If s/he will be unavailable to supervise this research personally, as when on sabbatical leave, s/he will arrange for an alternate Faculty Supervisor to assume direct responsibility in her/his absence and s/he will advise the IRB by letter in advance of such arrangements.

B. General Guidance

The HawkIRB system requires the investigator to respond to all applicable items on the New Project Application in order to submit the project to the HSO. Still, the most common problem with New Project applications is that not enough detail is provided for the IRB chair or members to evaluate the study’s purpose and/or procedures. In particular, investigators are encouraged to provide detailed information regarding how potential subjects are initially identified, and how consent is obtained. There is no such thing as providing too much detail when describing study procedures! The more complete the initial description is, the less likely that time will be spent with correspondence back and forth between the investigator and Human Subjects Office staff and/or IRB chairs to fill in the details. The New Project application in HawkIRB will guide you through what is required with regard to supporting documentation. In general, a complete submission for IRB review includes the following items as applicable:

• HawkIRB application
• Written protocol
• Reports of prior investigations that provide relevant information to the review
• Informed Consent Document(s) or other consenting materials
• Sample Informed Consent Document(s) (for example, the DHHS or other sponsor sample consent, if available).
• Recruitment materials
• Survey instruments
• Grant application
• Investigator’s Brochure
Other materials specific to the proposed study (e.g. sponsor correspondence with a regulatory agency such as the FDA regarding test article risk, etc.)

There are detailed instructions regarding how to attach your supporting documentation to the electronic application. Staff in the Human Subjects Office are available to respond to questions by e-mail or phone. We are also available to consult individually with you on how to use the HawkIRB system. Investigators with unique situations are encouraged to contact the Human Subjects Office.

C. Research Team

As part of the New Project Application, you will be asked to list all members of your research team for the project. You should include all individuals who have contact or interactions with research subjects or their private, identifiable information as research team members on your application.

For UI team members, you will be asked to provide the person’s name, e-mail address, department, the date the person complete human subjects protections training, and whether or not the individual will be a contact person for the project. If the person has completed human subjects protections training and is entered into our database, his/her certification date will show up automatically in HawkIRB. You will not be able to submit your application until all members of the research team have met this requirement. Information about how to obtain the required training can be found on the HSO website.

If there are personnel not affiliated with the University of Iowa (that is, they are not faculty, staff, or students of the UI) who will be conducting or are engaged in your research, they also need to have their activity reviewed by an IRB. If these individuals are not affiliated with an entity that has an IRB, you may be able to list them as a non-UI member of your research team. However there are additional procedural steps and documentation that need to be provided in your application in order for you to add non-UI personnel to the research team list on your application. Please refer to Chapter 9, Special Topics on Collaborative Research. Before adding non-UI personnel to your research team, you should first contact the HSO to discuss your situation.

D. Supporting Documentation

The New Project Application must be accompanied by some basic materials, when appropriate. HawkIRB will prompt you to attach materials based on your responses to questions in the application. As of May 1, 2007, you will be required to attach any required materials electronically. From that date forward, the ONLY hard copy document that will be accepted by the Human Subjects Office as supporting documentation for your application will be the signature page. If you only have a hard copy of your supporting documentation, you will need to use some means (for example, scanning the document) to convert the document to an electronic file so that it can be attached to the HawkIRB application. There are detailed instructions within HawkIRB that will guide you through attaching those materials. There are also some instructions regarding attachments on our HawkIRB FAQ page. Some of the materials that you may need to attach include:

- Informed Consent Documentation. Depending on your study, this may include: the standard ICD, the VAMC ICD, Record of Consent, Assent documents, Spanish short form documents, or the consent as a letter document. To create any of these documents, you will need to start with the template provided in HawkIRB, download them to your computer, make edits, and re-attach them to your HawkIRB application.

- Recruitment materials. These may include brochures, flyers, advertisements, audio-tapes, video-tapes, or other materials used to inform people about the study.
The complete grant proposal. This should include the budget pages and appendices.

The study protocol & sample consent, if available. If the study involves a clinical or therapeutic intervention, this may include a pharmaceutical company protocol or investigator-initiated study protocol. If available, the DHHS-sponsored or other sponsor sample consent should be included.

Data collection materials. This would include questionnaires, surveys, stimuli, etc., that will be used in the study.

Phone script(s). You will need to include these for situations that will involve providing information to potential participants via telephone.

For collaborations with non-UI entities:

Letter(s) of agreement. If you are collaborating with an outside agency, company or clinic and that non-UI entity is giving you access to its clients, files, or premises, you will need to attach a letter of agreement from that agency that confirms knowledge of the project's purpose and permission for the investigator to conduct the study there.

Individual Investigator’s Agreement. See the section in Special Topics on Collaborative Research.

For studies that require review by the Pharmacy & Therapeutics Committee or involve investigational drug interventions:

Investigator’s Brochure. You will need to attach a copy of the Investigator’s Brochure for the investigational drug under study.

Investigational New Drug (IND) number documentation. If the study involves an investigational drug, you will need to attach documentation of the IND number from the sponsor (if this is not indicated on the Investigator’s Brochure or protocol). In the case of investigator-held INDs, a copy of the FDA letter that informed the PI of the IND number.

G-12 form. If the study involves an investigational drug, or if FDA-approved drugs are being used off-label, you will need to fill out and attach a G-12 form.

For studies that require review by the Medical Radiation Protection Committee (MRPC):

The appropriate Radiation Protection Committee Research Application Form (either the regular or short form of this application).

E. Application Processing/Workflow

Once you have submitted your project through HawkIRB, it is automatically assigned an IRB Identification number. The IRB ID number remains with the study and is never reused. The IRB ID number appears on all correspondence, and on the approval stamp of the Informed Consent Document. A description of how you can track the progress of your application through HawkIRB is included on our HawkIRB FAQ page. Click on “Workflow: Tracking your Submitted Application.”

1. Admin Pre-Screening

All applications are screened by Human Subjects Office staff. At the pre-screening step, the application is being reviewed to ensure that the correct form has been used, all questions have been answered on the application, all attachments are present, etc. You may receive questions from the HSO staff at this step of the process requesting additional information or attachments.
The application is not considered “accepted” into our review process until the project moves out of this step and into the HSO Staff Review.

2. HSO Staff Review
At this step, the application is being given a more in-depth review by HSO staff prior to being sent to the Chair for review or before being prepared for a full board meeting.

3. IRB Review
Exempt or Expedited Review (IRB-Chair Review):
The IRB chairs (or his/her IRB member designee) determine whether the project is eligible for exempt status, expedited review, or requires full board review. If exempt or expedited review is appropriate, the chair or designated HSO staff may correspond with the investigator via HawkIRB with requests for additional clarification or materials prior to final approval. If the project is sent back to the PI, it is returned to the PI inbox and is noted in workflow as being under “PI review.” This means that it requires information/edits from the PI and that the PI has to send it back to our office through HawkIRB after the changes/additions have been made.

Full Board Review: (Pre-Meeting Prep, Scheduled, Post-Meeting Prep):
If the project requires full board review, the date of the full board review will be listed under the heading “Agenda Date” on the Project Summary page in HawkIRB. The HSO will notify the investigator if s/he is requested to attend the meeting. The HSO distributes copies of the Application Form, Informed Consent Document, and other supporting materials to members attending the meeting about a week in advance. The IRBs use a primary reviewer system, in which one IRB member is assigned the role of reviewing and presenting the study to the members at the full board meeting. If the study is potentially funded, the primary reviewer also reviews the grant application itself (or the pharmaceutical protocol and Investigator’s Brochure). The primary reviewer IRB member may contact the investigator for clarification prior to the meeting date. Any requests for revisions will come from the full board itself after the meeting.

In HawkIRB, when the project is ready to be scheduled to a full board meeting, it shows in workflow as “Pre-Meeting Prep.” At this stage, the application and materials are being prepared for a full board meeting. When the application moves in workflow to “Scheduled,” it has been scheduled to a meeting. You can check the date of the meeting by using the Project Summary page and looking under “Agenda Date.”

When the application moves to “Post-Meeting Prep,” the project has been reviewed by the full board and is now waiting for minutes from the meeting to be written and approved by an IRB chair. After the minutes are finalized by the IRB chair, they are sent to the Investigator and arrive in the PI's inbox.

F. Criteria for Approval
In order for the IRB (or IRB chair or his/her IRB member designee in the case of expedited projects) to approve a project, the following requirements must be satisfied [45 CFR 46.111 (DHHS) and 21 CFR 56.111 (FDA)]:

- Risks to subjects are minimized:
  (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and
  (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

- Risk/Benefit Ratio. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to
result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

- **Selection of subjects is equitable.** In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

- **Informed consent sought.** Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by [45 CFR 46.116 (DHHS) or 21 CFR 50 (FDA)].

- **Informed consent documented.** Informed consent will be appropriately documented, in accordance with, and to the extent required by [45 CFR 46.117 (DHHS) or 21 CFR 50.27 (FDA)].

- **Data safety monitoring.** When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

- **Protect privacy & maintain confidentiality.** When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

- **Vulnerable Populations.** When subjects are likely to be members of a vulnerable population, there are appropriate additional safeguards in place to protect the rights and welfare of these subjects.

**G. Revisions Prior to Final Approval**

For studies that are classified as **exempt or expedited**, the investigator must satisfactorily respond to all requests from the chair or his/her IRB member designee for revisions and/or clarification or additional information. The chair or his/her IRB member designee may approve projects as submitted or require modifications prior to approval. Chairs or their IRB member designee are not empowered to disapprove projects; in such cases, the application is submitted for full board review. When the chair or his/her IRB member designee determines all revisions have been made and that the study meets all criteria for approval, s/he approves the project and for expedited studies determines the interval for the next continuing review (not to exceed one year.)

For studies that require **full board review**, the investigator receives the meeting minutes electronically through HawkIRB. These minutes document the IRB's determinations. If the IRB requires minor revisions prior to final approval, the minutes will indicate that the study has been approved pending receipt of the required revisions with a designated timeframe for receipt of the revisions. Minor revisions include revisions to the protocol and/or application that are made by the IRB and require only a simple concurrence by the investigator(s). If the investigator(s) provide concurrence with the revisions, the IRB chair alone may review and approve the submitted revisions. If the investigator does not respond within the allotted time period, the application may be withdrawn from further consideration. If the investigator wishes to pursue the project at a future date, s/he would then need to submit another New Project application, incorporating comments from the prior IRB review.

If the IRB requires revisions that require more than simple concurrence of the investigator(s), the minutes will indicate that the study has been tabled. The investigator must respond in full to all issues raised by the IRB prior to the project being returned to the full board for further review.
In the HawkIRB workflow, you may see the following categories in regard to your project after it has been reviewed by the full board:

- **Approved Pending.** This means that the application is approved pending revisions and response by the PI as indicated in the minutes. The PI/delegate(s)/contact persons on the research team receive an e-mail notification by HawkIRB of this status. The application is routed to the PI and requires a response from the PI prior to final approval.

- **Tabled.** This means that the application was tabled at the meeting pending revisions and clarifications by the PI. The PI/delegate(s)/contact persons on the research team receive an e-mail notification by HawkIRB of this status. The application is routed to the PI and requires a response from the PI prior to being scheduled to a future full board meeting.

- **Disapproved.** This means the application was disapproved after review by the full board. The PI/delegate(s)/contact persons on the research team receive an email notification by HawkIRB of this determination.

- **Withdrawn.** For all applications EXCEPT for Reportable Event Forms (REFs), this means the application has been withdrawn, either at the request of the PI, or by the IRB if the PI failed to respond in a timely manner to requests for more information. The PI/delegate(s)/contact persons on the research team receive an email notification by HawkIRB of this status.

- **Withdrawn. (REFs only).** This means that the reported event submitted on the REF did not meet the criteria for reporting to the IRB. To review these criteria, refer to Chapter 7, Section C.

- **Approved.** This means the application has been approved and is waiting for final processing in the HSO before being released to the PI. When the project is released, the PI/delegate(s)/contact persons on the research team will receive an email notification.

**H. Notification of Approval**

Upon receipt of final approval by the IRB chairs, HawkIRB automatically stamps approved Informed Consent Document(s) and other materials (e.g. letters to subjects, ads) with the IRB ID number, the date of approval, and the date of expiration. This stamp is typically in the upper right corner of the document. Questionnaires and data collection forms are generally not stamped. The system notifies the PI and designated members of the research team of the approval and allows access to currently approved documents.

Ultimately, it is the Principal Investigator's responsibility to maintain accurate files of IRB correspondence, approvals, and research records for three years following the close of the study. With the advent and use of HawkIRB, this process should be much simpler for investigators as all correspondence and IRB documentation related to the project is available electronically through the HawkIRB application.

The investigator has access to an electronic approval memo in HawkIRB. The approval memo includes the type of review (full board, expedited, or exempt), date of next continuing review, and a summary of investigator responsibilities. This memo reminds investigators that changes in research activity may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to subjects.

There is also a statement within HawkIRB that the approved project was electronically signed by the IRB chair. This statement includes the name of the chair and the date and time of the electronic signature.

**Please Note!**
The PI and research staff are required to use the currently approved, stamped consent documents when enrolling research subjects unless a documented exception has been granted by the IRB.

There are some issues for final release of the approval for projects that have external funding. If your study is funded by a government or non-profit agency, you will also receive an "Assurance Identification/IRB Certification/Declaration of Exemption" (NIH 310) form for new project, continuing review, and modifications adding new funding sources. This form will be sent to either your sponsor directly or to you in a separate campus mailing from Sponsored Programs. It will contain the same date as the IRB approval memo, and will be signed by the Institutional Official. It indicates the IRB ID number, PI Name, Project Title, sponsoring agency or organization, and other information about the type of IRB review.

If the project is industry sponsored, the IRB approval is not released to the investigator until the contract has been finalized by the Clinical Trials Office.

I. Limitations on IRB-Approved Projects – Rules to Understand before you begin

Your Approval is Limited to your specified procedures

An approved project is limited in its conduct to the recruitment activities and study procedures that were described in the initial New Project application. In other words, the investigator may perform only those activities that s/he described. If the investigator wishes to change the study recruitment activities or procedures from what was initially described, s/he should submit a Modification/Update application for IRB review and approval prior to implementation (see next chapter for more information on Modification/Update applications).

Your Approval is for a Limited Time Period

Each project is approved for a specified period of time and research activity may not continue beyond that date without approval of a Continuing Review application (see next chapter for more information on Continuing Review applications). The Approval documentation indicates the due date for the next continuing review. The IRB may require that review occur more frequently than annually, for example after the first several subjects have been enrolled. Such determinations are documented in the full board meeting minutes sent to the investigator. In such cases, it is the investigator's responsibility to submit a Continuing Review application after the specified number of subjects or prior to the specified time period.

You are Approved to Enroll a Limited Number of Subjects

All projects are approved to enroll only the number of subjects indicated in the New Project application. If the investigator finds that actual enrollment is approaching that limit, a Modification application should be submitted requesting an increase in the number of subjects to be enrolled in the study. The application must be approved before additional subjects may be enrolled beyond the originally approved number.

When is a subject considered enrolled?

An enrolled subject is anyone who has signed an Informed Consent Document, whether or not that individual actually completes the study. Thus, someone who signs a consent document but is determined during screening to be ineligible, or chooses not to continue, must still be counted as an enrolled subject.

You are Limited to the use of your Currently Approved Consenting Materials

Finally, only the current, approved Consent Document may be used for documenting informed consent. Documenting consent on a Consent Document on or after the expiration date stamped on that Document is not permitted and may not constitute valid consent. With each Continuing
Review, the investigator receives newly-stamped versions with the approval notification. Even if the content is identical, you are expected to use the current, stamped version of all stamped materials.

J. Appeal of IRB Decisions

Investigators may appeal the IRB requirement for specific changes in the protocol and/or consent documents(s). If the application is being reviewed under expedited procedures, the Chair works directly with the investigator to resolve outstanding issues. Such appeals are documented as responses in the HawkIRB system or via e-mail to the Chair. If the Chair and investigator cannot resolve the issue(s), the project is referred to full board for review.

If the full board IRB decides to require specific changes or to disapprove a research activity, the minutes from the meeting provides the reasons for its decision. The investigator may appeal any of the requested changes or the disapproval. Such appeals should be submitted in writing via HawkIRB as a response to the meeting minutes. Such appeals must be reviewed at a full board meeting. The basis for appeals must include new information that was not previously submitted to or considered by the IRB. The investigator should provide a rationale for the appeal and any other relevant supporting documentation. If the appeal requires discussion or explanation beyond what is provided to the board in written format, the investigator may be invited by the Chair to attend the full board meeting at which the appeal is presented. The investigator is invited for the purpose of answering questions and participating in discourse with board members. The investigator will leave prior to IRB discussion and vote on the issues. The IRB will notify the investigator in writing via the meeting minutes of the discussion and vote on the appealed issue(s).

In the case of a decision by the IRB to disapprove, suspend, or terminate a project, the decision may not be reversed by any other person or entity including the Associate Vice President for Research, or any other officer/agency of the University of Iowa, state government, or federal government.

K. Other University Committees Reviewing Human Subjects Research

The University of Iowa Institutional Review Boards coordinate reviews with other institutional committees as described on the Human Subjects Office web page. None of these committees are a formal part of the University of Iowa IRB structure, but there is communication between the committees regarding status of review and/or conditions of approval.

Other committees that review human subjects research applications include:

- **Conflict of Interest in Research Committee (CIRC)**
- **General Clinical Research Center Advisory Committee (GAC)**
- **Holden Comprehensive Cancer Center Protocol Review & Monitoring Committee (PRMC)**
- **Institutional Biosafety Committee (IBC)**
- **Medical Radiation Protection Committee (MRPC)**
- **Nursing Research Committee (NRC)**
- **Pharmacy and Therapeutics Committee (P&T)**
- **VAMC Research and Development Committee (VAMC)**

Final IRB review is held for the review and determinations of the IBC, the PRMC, and the CIRC. Final IRB approval (but not review) is held for the review and determinations of the MRPC & P&T Committees. Neither IRB review nor approval is held for the determinations of the VAMC R&D Committee, the GAC or the NRC.

Information regarding these committees, and a contact person for each, is available by clicking on the above links.
Chapter 7 – After Initial IRB approval.

As an investigator, you have a variety of IRB communication and record-keeping responsibilities after your research project is initiated. Major responsibilities are described below. You may also have additional responsibilities from your funding agency or other regulatory agencies.

A. Modifications

Any change in the conduct of a study must be reviewed and approved by the IRB prior to implementing the change. The exception to this is when the change is necessary to eliminate apparent immediate hazards to subjects. The investigator is required to promptly notify the IRB of any changes made without IRB approval to eliminate apparent immediate hazards to subjects using the Modification Form as described below. The convened IRB will review these modification forms to determine that any changes made by the investigator to eliminate apparent immediate hazards to the subjects were consistent with ensuring the subjects’ continued welfare. Your approval memo notifies you of this responsibility.

Modifications include, but are not limited to:
- procedural changes to a protocol,
- adding or removing investigators or research team members,
- changing the title of the project,
- requesting additional subjects beyond the original approved number,
- change in funding sources,
- changes in how you are recruiting or following subjects.
- new or revised advertisements,
- changes to Informed Consent Documents, surveys, questionnaires, correspondence with potential or current subjects, or additional new items,
- protocol changes.

Modifications to an approved project should be submitted on a Modification/Update Form. If your project was initiated in HawkIRB or you have transferred the project to the HawkIRB system via the legacy project transfer at your continuing review, you will need to submit modifications through the HawkIRB system. You may submit a modification at the same time as a continuing review. Instructions for the completion of these applications are contained within the HawkIRB system.

Minor modifications are modifications to a research project and/or consent documents that pose no additional risk to subjects (e.g. changes in title, co-investigator(s), funding sources). If the modification is an addition or modification of procedures they must fall into one of the categories eligible for expedited review. To be considered a minor modification, it must also maintain similar or increased safeguards to protect the subject. These minor modifications may be approved by the chair or his/her IRB member designee alone using the expedited review procedure. More extensive modifications may require full board review. In either case, revisions or clarifications may be required.

All modifications must be approved by the IRB prior to implementation.

Once a PI has received a protocol amendment from a study sponsor, it is the PI's responsibility to submit the amendment in a timely manner for IRB review and approval. Based on guidance from the FDA, potential subjects who meet eligibility criteria under a pending amendment to the protocol may not be enrolled until after the amendment is approved by the IRB. Further, the FDA will hold the PI responsible for compliance with this requirement. The sponsor does not
have the authority to override this FDA regulation, and therefore it is inappropriate for the PI to request "special permission" from the sponsor to implement any aspect of the amendment before IRB approval. Rather, the PI should move as quickly as possible towards submitting the amendment for IRB approval.

On occasion the IRB receives questions about whether or not "protocol violations" or "protocol deviations" need to be reported to the IRB. Please refer to Section C of this chapter for more information on reporting requirements.

B. Continuing Review

The IRB is required to review and approve all non-exempt research projects at intervals appropriate to the degree of risk, but not less than once a year [45 CFR 46.109(e) (DHHS) and 21 CFR 56.109(f) (FDA)]. This is called "continuing review." Continuing review for non-exempt research is required to occur as long as the research remains active for long-term follow-up of the research subject, even when the research is permanently closed to the enrollment of new subjects and all subjects have completed all research-related interventions and to occur when the remaining research activities are limited to collection of private identifiable information.

As described above, the Informed Consent Document(s) indicate the project's expiration date. If a project initially received expedited review and risks to subjects remain minimal, the continuing review may be expedited (reviewed by the chair alone). If a project initially received full board review, the project generally requires full board continuing review. Investigators are encouraged to allow three to four weeks from date of submission for full board review and approval. A schedule for full board continuing review of IRB-01 projects is available on the HSO web site.

Due date for submitting an application for continuing review

It is the Principal Investigator's responsibility to submit an application for continuing review in sufficient time to permit the IRB chair or full board to review and approve the application prior to its expiration date. As a service to investigators, the HawkIRB system sends the reminders to the Principal Investigator, and all contact persons listed for a given application. The reminder schedule is based on the Last Possible Submission Date (LPSD) of the project. The LPSD is the date that you need to have your project submitted to our office to ensure that you can obtain review and approval prior to the project expiration date. You will receive automated reminders on the following schedule:

- A reminder memo is sent via email 30, 14, 7 and 1 day before the LPSD of the project.
- On the day of the LPSD (if a continuing review application has not yet been received by the HSO) you will receive notice by email that there will not be sufficient time prior to the expiration of the project for review and approval. This notice will state that IRB approval will lapse as of 12:01 a.m. on the expiration date and no further research activity may occur on or after that date. You will be asked to submit your continuing review application or close the project.
- **NO HUMAN SUBJECTS ACTIVITY (which includes the enrollment and follow-up of subjects and the collection and/or use of research data) MAY TAKE PLACE ON OR AFTER THE EXPIRATION DATE** unless there is an over-riding safety concern (as determined by an IRB Chair) and until you receive approval of your continuing review application.
- On the day prior to the date of expiration, you will receive notice that your project will lapse and that no human subjects activity may take place after 12:01 a.m. on the expiration date. You will have 10 working days from the date of this notice to obtain review
and approval of the continuing review for the project or it will be administratively closed by
the IRB through the Human Subjects Office.

If the HSO closes the study due to no response, the HSO sends the investigator a notification
via email of study closure. The investigator's departmental executive officer (DEO) may also
receive notification of closure. In cases of on-going externally funded projects, the Division of
Sponsored Programs or the Clinical Trials Office also receives a copy of the closure notice and
make an independent determination regarding the need to notify the sponsor. Once the HSO
closes a project, the only way for the project to resume is for the investigator to submit a New
Project Application (via the HawkIRB system) for IRB review and approval.

How to submit a continuing review application

If you started your new project in HawkIRB or transferred your project to HawkIRB from the
paper system, the continuing review information should be submitted via HawkIRB. You should log
onto the HawkIRB system and choose your open project from your inbox. From there, you can
choose to open either of the following forms:

- Continuing review form [Use this form if you are not submitting a modification/update in
  conjunction with your continuing review]
- Modification/Update + Continuing Review Form.

Instructions for completing and submitting the forms are within each HawkIRB application.

Review and Approval Process for Continuing Reviews

Procedures for expedited or full board review, criteria for approval, and revision prior to
approval, are identical to those described above for New Projects. Notification of approval of a
Continuing Review form is identical to that described for New Projects.

C. Other Reporting Requirements for Investigators

The following list are events that are reportable by UI investigators to the UI IRB:

1) Any unanticipated problems involving risks to subjects or others which occurs at the UI or
that impacts UI subjects or conduct of the UI study.
2) A serious adverse drug event (either expected or unexpected) occurring in a UI subject.
3) A serious adverse device effect (either anticipated or unanticipated) occurring in a UI
subject.
4) An unanticipated serious adverse device effect occurring in a non-UI subject.
5) Receipt of new information (including risk or benefit) that may impact the willingness of
subjects to participate or continue participation in the research study.
6) Any incidents of noncompliance with the federal regulations or the requirements or
determinations of the IRB.

Investigators are required to report to the appropriate UI IRB if any of the above items #1-6
occur in a study where IRB-01 or IRB-02 is the IRB of record. (For WIRB studies, items #1-6 are
reportable directly to WIRB. For studies reviewed under CIRB procedures, items #1-3 and #6 are
reportable to both IRB-01 and the CIRB while items #4-5 are reportable only to the CIRB).

What are unanticipated problems involving risk to subjects or others?
An unanticipated problem involving risks to subjects or others is any event or problem that:

- was not expected given the nature of the research, the population under study and the
  approved procedures or protocol for the conduct of the study,
impacts the rights, safety, or welfare of subjects or others (e.g. those not directly involved in the research such as research staff or family members), AND

is related to the research intervention, research procedures, and/or conduct of the research study.

**What is a serious adverse drug event?**

A serious adverse drug event is any adverse drug experience (associated with the use of the drug) occurring at any dose that results in any of the following outcomes:

- death,
- life-threatening adverse drug experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

**What do you mean by an unexpected adverse drug event?**

This would be any adverse drug experience (associated with the use of the drug), the frequency, specificity, or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information provided to the subjects and the IRB.

**What is an unanticipated adverse device effect?**

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death the frequency, specificity, or severity of which has not previously been identified in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

**What do you mean by noncompliance?**

Noncompliance is a failure to follow the federal regulations with respect to protection of human subjects in research or failure to follow the determinations of the IRB with respect to conduct of the research as approved by the IRB.

1. **Unanticipated Problems Involving Risks to Subjects or Others Which Occur at UI or That Impact UI Subjects or Conduct of the UI study.**

An unanticipated problem involving risks to subjects or others has been defined above. Examples of unanticipated problems involving risks to subjects or others include a breach of confidentiality, a subject complaint when the complaint indicates unexpected risks or cannot be resolved by the investigators, a research team member experiences harm in the conduct of the study, a new risk of the study drug, device, or study procedure is identified by an outside source (sponsor, federal regulatory agency, outside site, etc.) When a research study includes investigational drugs or devices, some unanticipated problems may also meet the definition of an unexpected adverse drug experience (serious or otherwise), or an unanticipated adverse device effect.

Investigators must report any unanticipated problem involving risk to subjects or others using the Reportable Event Form (REF) in the HawkIRB system. This form includes a description of the event, the date of occurrence, whether it is a local or outside report, how the event affected the
rights, safety or welfare of the subject or others, current status of UI subjects, and any planned changes or modifications to the project as a result of the event. Reports from the investigator to the IRB must be submitted via HawkIRB within ten working days of the event or notification to the investigator of the event.

The IRB chair compares the content of the REF with the previously approved project materials such as applications, informed consent document(s), protocols, investigator brochures, or other supporting documents to determine whether this event meets the definition of an unanticipated problem involving risk to subjects or others. If the chair agrees the event meets the definition of an unanticipated problem involving risks to subjects or others, the chair determines whether the event represents minimal risk of harm or more than minimal risk of harm to subjects enrolled under the UI study. If the event represents minimal risk of harm, the chair reviews and signs the report through the HawkIRB system. If the event represents more than minimal risk of harm to subjects enrolled under the UI study, the report is referred to the convened IRB for review.

All reports of unanticipated problems involving risks to subjects or others are electronically filed with the appropriate research study. These reports are also reviewed by the IRB at the time of continuing review. Reports of all such problems for all projects reviewed by the Chair or convened IRB are provided by e-mail to all IRB-01 or IRB-02 members as appropriate on a monthly basis.

2. Serious adverse drug event (either expected or unexpected) occurring in a UI subject.

If a subject is enrolled by UI investigators, the investigator must report to the UI IRB either serious adverse drug events or unexpected adverse drug events. By definition, these events must be associated with the use of the drug.

Investigators must report any serious adverse drug event using the Reportable Event Form (REF). This form includes a description of the event, the date of occurrence, the type of risk, whether the event was unexpected, the outcome, and an assessment of degree of relatedness to the research. The form also includes the proposed actions to be taken by the investigator with regard to modifying approved study materials (including change in consent documents or other notification procedures) and notifying current subjects. Reports from the investigator to the IRB must be submitted via HawkIRB within ten working days of the event or notification to the investigator of the event.

Reports of serious and expected adverse drug events occurring in a UI subject are reviewed by an IRB Chair to verify that the event would be considered “expected” based on the information previously reviewed and approved by the IRB. If the Chair verifies that this information is correct, the Chair signs the report through the HawkIRB system.

All reports of serious and unexpected adverse drug events occurring in a UI subject are reviewed by the UI IRB Chair and/or the UI IRB in the following manner. The IRB chair compares the content of the REF with the previously approved project materials such as applications, informed consent document(s), protocols, investigator brochures, or other supporting documents to determine whether this event meets the definition of an unanticipated problem involving risk to subjects or others. If the chair agrees the event meets the definition of an unanticipated problem involving risks to subjects or others, the chair determines whether the event represents minimal risk of harm or more than minimal risk of harm to subjects enrolled under the UI study. If the event represents minimal risk of harm, the chair reviews and signs the report through the HawkIRB system. If the event represents more than minimal risk of harm to subjects enrolled under the UI study, the report is referred to the convened IRB for review. The full board determines whether subjects must be notified of the new information, and if so, the method of notification and whether any study materials (e.g. consents, protocol) must be updated to reflect the new information.

All reports of serious adverse drug events occurring in a UI subject are electronically filed with the appropriate research study. These reports are also reviewed by the IRB at the time of
continuing review. In addition, reports of all serious adverse drug events for all projects reviewed by the Chair or full board IRB are provided by e-mail to all IRB-01 members on a monthly basis.

In addition to the above requirements, investigators conducting human gene therapy research must submit a written report of serious adverse experiences that are unexpected and associated with the use of the gene transfer product to the NIH Office of Biotechnology Activities (NIH/OBA), the U of I Institutional Biosafety Committee, the IRB, and the FDA or study sponsor within specified timeframes as found in Appendix M-I-C-4 in the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines). Gene therapy investigators must submit annual reports to OBA as set forth in Appendix M-I-C-3 of the NIH Guidelines.

3. Serious adverse device effects (either anticipated or unanticipated) occurring in a UI subject.

If a subject is enrolled by UI investigators, the investigator must report either serious adverse device effects or unanticipated adverse device effects. By definition, these effects must be associated with the use of the device.

Investigators must report any serious adverse device effect occurring in a UI subject to IRB-01 using the Reportable Event Form (REF). This form includes a description of the effect, the date of occurrence, the type of risk, whether the effect was unanticipated, the outcome, and an assessment of degree of relatedness to the research. The form also includes the proposed actions to be taken by the investigator with regard to modifying approved study materials (including change in consent documents or other notification procedures) and notifying current subjects. Reports from the investigator to the IRB must be submitted via HawkIRB within ten working days of the event or notification to the investigator of the event.

Reports of serious and anticipated adverse device effects occurring in a UI subject are reviewed by an IRB Chair to verify that the effect would be considered “anticipated” based on the information previously reviewed and approved by the IRB. If the Chair verifies that this information is correct, the Chair signs the report through the HawkIRB system.

Reports of serious and unanticipated adverse device effects occurring in a UI subject are reviewed by the UI IRB Chair and/or UI IRB in the following manner. The IRB chair compares the content of the REF with the previously approved project materials such as applications, informed consent document(s), protocols, investigator brochures, or other supporting documents to determine whether this event meets the definition of an unanticipated problem involving risk to subjects or others. If the chair agrees the event meets the definition of an unanticipated problem involving risks to subjects or others, the chair determines whether the event represents minimal risk of harm or more than minimal risk of harm to subjects enrolled under the UI study. If the event represents minimal risk of harm, the chair reviews and signs the report through the HawkIRB system. If the event represents more than minimal risk of harm to subjects enrolled under the UI study, the report is referred to the convened IRB for review. The full board determines whether subjects must be notified of the new information, and if so, the method of notification and whether any study materials (e.g. consents, protocol) must be updated to reflect the new information.

All reports of serious adverse device effects occurring in a UI subject are electronically filed with the appropriate research study. These reports are also reviewed by the IRB at the time of continuing review. In addition, reports of all serious adverse device effects for all projects reviewed by the Chair or full board IRB are provided by e-mail to all IRB-01 members on a monthly basis.

4. Unanticipated serious adverse device effects occurring in a non-UI subject.

FDA regulations (21 CFR 150(b)(1)) require the sponsor to report the results of any evaluation of an unanticipated serious adverse device effect to all reviewing IRBs and participating investigators. Any such reports are initially received by the UI investigator who is in turn
responsible for reporting this information to the UI IRB-01. By definition, these effects must be associated with the use of the device.

Investigators must report any evaluation of unanticipated serious adverse device effects conducted by the sponsor occurring in a non-UI subject to IRB-01 using the Reportable Event Form (REF). This form includes a description of the effect, the date of occurrence, the type of risk, the outcome, and an assessment of degree of relatedness to the research. The form also includes the proposed actions to be taken by the investigator with regard to modifying approved study materials (including change in consent documents or other notification procedures) and notifying current subjects. Reports from the investigator to the IRB must be submitted via HawkIRB within ten working days of the event or notification to the investigator of the event.

All reports of unanticipated serious device effects occurring in a non-UI subject are reviewed in the following manner. The IRB chair compares the content of the REF with the previously approved project materials such as applications, informed consent document(s), protocols, investigator brochures, or other supporting documents to determine whether this event meets the definition of an unanticipated problem involving risk to subjects or others. If the chair agrees the event meets the definition of an unanticipated problem involving risks to subjects or others, the chair determines whether the event represents minimal risk of harm or more than minimal risk of harm to subjects enrolled under the UI study. If the event represents minimal risk of harm, the chair reviews and signs the report through the HawkIRB system. If the event represents more than minimal risk of harm to subjects enrolled under the UI study, the report is referred to the convened IRB for review. The full board determines whether subjects must be notified of the new information, and if so, the method of notification and whether any study materials (e.g. consents, protocol) must be updated to reflect the new information.

All reports of unanticipated serious adverse device effects occurring in a non-UI subject are electronically filed with the appropriate research study. These reports are also reviewed by the IRB at the time of continuing review. In addition, reports of all unanticipated serious adverse device effects for all projects reviewed by the full board are provided by e-mail to all IRB-01 members on a monthly basis.

5. Receipt of new information (including risk or benefit) that may impact the willingness of subjects to participate or continue participation in the research study.

During the course of a study, researchers may become aware of new information that would impact a subject’s decision to participate, or continue participating in the research study. For example, interim analyses of data may identify a trend which impacts the safety of subjects, or may identify early efficacy (benefit) of one of the interventions under study. In addition, results from other research studies or changes in standards of practice or care may affect conduct of a study and would need to be communicated to research subjects.

Investigators must report any new information that may impact the willingness of subjects to participate to either IRB-01 or IRB-02 using the Reportable Event Form (REF). This form includes a description of the new information and its potential impact on subjects. Reports from the investigator to the IRB must be submitted via HawkIRB within ten working days of the event or notification to the investigator of the event. In addition, a modification form must be submitted describing the investigator’s proposed method for providing this information to subjects.

Reports and modifications related to new information are reviewed by an IRB Chair to determine if the method and information provided to subjects is appropriate. If the Chair verifies that this information is correct and notification is appropriate, the Chair signs the report and modification through the HawkIRB system. The Chair refers the review to the full board when s/he believes the information or notification method is not appropriate, or if the new information significantly impacts the safety of current or potential subjects. When protocol changes are
immediately required to eliminate apparent immediate hazards to subjects, the Chair may approve
notifications prior to full board review.

6. Noncompliance with Federal Regulations or the Requirements or Determinations of the
IRB
Investigators who are self-reporting noncompliance with federal regulations or the
requirements or determinations of the IRB to IRB-01 or IRB-02 use the Reportable Event Form
(REF). This form includes a description of the noncompliance and description of impact on the
rights, safety, or welfare of subjects or others. Reports from the Investigator to the IRB must be
submitted via HawkIRB within ten working days of the event or notification to the investigator of
the event.

Others may report noncompliance as described in Chapter 10 of this Guide. All reports of
noncompliance, regardless of the source are reviewed by the IRB Chair and/or UI IRB according
to the procedures described in Chapter 10 of this Guide.

D. Monitoring Program
Additional monitoring of approved projects occurs on a continual basis. The IRB monitors are
full-time HSO staff who conduct random, study initiation, and directed monitoring visits of
research. The monitoring program includes studies reviewed by IRB-01, IRB-02, WIRB, and CIRB.
The main goals of this program are to assess and enhance the protection of human subjects
involved in research. This is accomplished by providing education to investigators and their
research team and determining, from a source other than the investigator's continuing review
report that no material changes have occurred in the project since the previous IRB review. In
addition to the regular monitoring staff, IRB members, or other professional staff in the Human
Subjects Office acting on behalf of the IRB, may conduct monitoring activities.

Reason(s) for on-site review may include, for example:
1. random selections,
2. complex projects involving unusual levels or types of risks to subjects,
3. projects involving vulnerable populations,
4. projects conducted by an investigator who previously failed to comply with IRB
determinations,
5. projects where continuing review or reports from other sources have indicated that
changes without IRB approval may have occurred.

For random and study initiation reviews, the research monitors meet with research team
members to review and assess the following areas:

- Research team composition
- Recruitment and consent procedures
- Study procedures and expected study end
- Study reports from outside monitoring entities such as Data Safety Monitoring Boards,
  Contract Research Organizations, and publications from the study
- Current enrollment and verification of consent
- Adverse events, unanticipated problems, receipt of new information, and issues of
  noncompliance
- Storage of study documents and data
- Privacy and confidentiality issues
- Data analysis
- Drug/Device accountability
- Staff training and communication
Subject payment

The conduct of an on-site review may include any or all of the following:

1. requests for progress reports from investigators,
2. examinations of research records, including signed Informed Consent Documents, protocol amendments, and serious and/or unexpected adverse experience reports,
3. contacts with research subjects,
4. observation of the consent process.

Examples of when observation of the consent process could occur are: 1) the full board IRB determines during review of a project that a conflict of interest exists such that the informed consent process should be observed by a neutral party; 2) the IRB is made aware of a complaint or concern with regard to the informed consent process; or 3) the IRB determines as a result of the monitoring process that the consent process is insufficient and education/training is required for conduct of consent.

A draft report of the findings of random monitoring visits is written by the monitor and e-mailed to the PI and copied to other research team members as appropriate within two weeks of the monitoring visit. The PI is asked to reply regarding any comments or on the accuracy of issues described in the report within 2 weeks of receipt. If the PI does not reply in this time frame, the report is considered to be accurate and it is forwarded to an IRB Chair for review. Any responses are incorporated into a final report to the Chair of the monitoring visit. The Chair reviews and approves the report or requests changes to the required actions based on the information provided. If any of the findings require full board review as designated in the IRB Monitoring Guidelines, the report is referred to the next available Executive IRB-01 meeting or regular full board meeting (IRB-02) for review. If none of the items require full board review, the final approved report is e-mailed to the PI and research team and response is required within two weeks. If the PI does not respond in this timeframe, the PI is sent a letter by e-mail indicating they must respond within 2 weeks or the report may be sent to the full board for consideration of study suspension until the issue is resolved.

Following study initiation visits the monitor completes a checklist and notes any issues which need to be addressed by the research team. The checklist is e-mailed to the PI with copies to the research team as appropriate and the IRB Chair within two weeks of the visit. If the PI needs to respond to an item, the checklist first is reviewed by the Chair for approval. The PI is then given two weeks to respond to the required action. If the PI does not respond in this timeframe, the PI is sent a letter by e-mail indicating they must respond within 2 weeks or the report may be sent to the full board for consideration of study suspension until the issue is resolved.

Directed monitoring visits may include any of the items above or other specific investigation as requested by the IRB Chair or IRB. The monitor generates a written report within two weeks following these visits based on the information requested. The Chair determines if any findings constitute noncompliance. If so, the procedures described in Chapter 10 of this Guide are followed. If the findings do not constitute noncompliance, the Chair resolves the issues directly with the research team when the issues involve no or minimal risk to subjects or others. If the issues involve more than minimal risk to subjects or others, the report is forwarded to the next Executive IRB-01 meeting or regular full board meeting (IRB-02) for review.

A written record of these activities is maintained in the study file and in the HSO office.

E. Project Closure
When should I close my project with the IRB?

When a study ends, is closed, or canceled for any reason, you must complete a Project Closure Form. A Project Closure Form serves as notification to the Human Subjects Office that IRB continuing review of the study is no longer needed.

If no subjects have been enrolled in a study for a period of three or more years, the IRB may require that the project be closed, unless there are extenuating circumstances for keeping the project open (e.g., the study is about a rarely-seen condition). *Take care not to close the project too soon! Once a Project Closure Form is submitted, no more data may be collected about any of the subjects in the study and no more contact with subjects for research purposes is allowed. There is no mechanism to re-open a closed study.* Therefore, if an investigator is still collecting follow-up data about subjects (either directly from subjects or indirectly from existing records), the project should remain open until all data have been collected, even if new subjects are no longer being enrolled.

How do I submit a project closure?

If your project was started in the HawkIRB system or has been transferred to the HawkIRB system, you should use HawkIRB to close the project. Log-on to HawkIRB and choose the project you wish to close. Choose the “Project Close Form” and follow the directions to submit the project closure. *Take care not to close the project too soon! Once a Project Closure Form is submitted, no more data may be collected about any of the subjects in the study and no more contact with subjects for research purposes is allowed. There is no mechanism to re-open a closed study.*

F. Record Keeping

What (if any) IRB related documentation do I need to keep?

Every principal investigator is required by University and federal regulations to maintain records of all correspondence relating to the use of human subjects in research. Copies of the Human Subjects application forms, notices of approval, and signed Informed Consent Documents must be maintained in the investigator's records. All records of human subject research are subject to inspection by federal authorities and the University of Iowa IRB.

How long do I have to keep records pertaining to my research?

Copies of all research records must be kept for **three years after the close of the study**. Studies that involve drugs or devices seeking FDA approval must be kept for two years after the FDA has taken final action on the marketing application.
Chapter 8 – Vulnerable Populations

Federal regulations involving human subjects in research include specific protections for children, pregnant women and fetuses, and prisoners. In addition, the IRB expects the investigator to provide additional information regarding cognitively impaired individuals in research as well as indicate in the application any other populations that the investigator might consider to be particularly vulnerable in a research setting. Examples of these additional types of vulnerable populations include those persons who are educationally or economically disadvantaged, students (see Chapter 5, Section E1 of this Guide for more information regarding students in research), or other groups that may require special consideration.

A. Pregnant Women, Human Fetuses and Neonates

Federal regulations direct that IRBs require additional safeguards before approving research involving fetuses, pregnant women, or neonates (45 CFR 46, Subpart B).

The IRB may approve research involving pregnant women or fetuses if all of the following conditions are met:

a) where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

b) the risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means;

c) any risk is the least possible for achieving the objectives of the research;

d) if the research holds out the prospect of direct benefit to the pregnant woman, the prospect of direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, the woman’s consent is obtained OR

e) if the research holds out the prospect of direct benefit solely to the fetus, then the consent of the pregnant woman and the father is obtained except that the father’s consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest;

f) each individual providing consent under (d) or (e) is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

g) for children who are pregnant, assent and permission are obtained in accord with the regulations for children in research;

h) no inducements, monetary or otherwise, will be offered to terminate a pregnancy;

i) individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

j) individuals engaged in the research will have no part in determining the viability of the neonate.

Neonates, neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

a) where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates;

b) each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate;
c) individuals engaged in the research will have no part in determining the viability of the neonate;
d) the requirements regarding neonates of uncertain viability (see below) or nonviable neonates (see below) have been met as applicable.

**Neonates of uncertain viability.** Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research unless the following additional conditions have been met:

1. The IRB determines that:
   i) the research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective; or
   ii) the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research.

   AND

2. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent’s legally authorized representative is obtained (except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest).

**Nonviable neonates.** After delivery nonviable neonates may not be involved in research unless all of the following additional conditions are met:

1. vital functions of the neonate will not be artificially maintained;
2. the research will not terminate the heartbeat or respiration of the neonate;
3. there will be no added risk to the neonate resulting from the research;
4. the purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
5. the legally effective informed consent of both parents of the neonate is obtained (note: waiver or alteration of the consent does not apply here) If either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of the legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements.

**Viable neonates.** A neonate, after delivery, that has been determined to be viable may be included in the research only to the extent permitted by and in accord with the requirements for children involved in research (see Section C below).

Research not otherwise approvable will only be allowed in this vulnerable population if:

(a) the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates; AND

(b) the Secretary of DHHS, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following an opportunity for public review and comment, including a public meeting announced in the Federal Register has determined that the research may take place.
Research involving human fetal tissue (placenta, or tissue from a spontaneous or induced abortion or from a still birth) is evaluated as tissue specimen research, using the guidelines for research involving specimens. Studies using human fetal tissue for transplantation research and studies of human embryos involve very explicit regulations concerning consent and study procedures. Investigators wishing to conduct transplantation research with human fetal tissue should contact the Human Subjects Office well in advance of IRB application submission to discuss applicable regulations.

B. Prisoners

Because incarceration could affect a person’s ability to make a truly voluntary and uncoerced decision whether or not to participate in a research project, the federal regulations provide additional safeguards for the protection of prisoners (45 CFR 46, Subpart C). A prisoner is defined as any individual involuntarily confined or detained in a penal institution. This definition includes individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

At the University of Iowa, any project that recruits prisoners must be reviewed at a full IRB meeting with a prisoner advocate present. If the project was not initially approved to recruit prisoners, then the investigator may not enroll a prisoner (e.g., a prisoner who is brought to UIHC for treatment who happens to be eligible for a research study may not be enrolled unless the "prisoner box" was checked on the initial application face page and the project was reviewed at a full board meeting with a prisoner advocate present.)

The prisoner rules also apply for a subject who at a later date becomes a prisoner, because it is unlikely that the IRB review of the research project contemplated the constraints imposed by incarceration. Therefore, if an investigator determines that a subject has become a prisoner at some later date after enrollment, and the study involves additional research interventions or interactions with that subject, the subject must either be dropped from follow-up, or a modification application must be submitted requesting review for inclusion of prisoners as subjects.

When a prisoner is a subject, in addition to the usual criteria for approval, the IRB must find that:

1) the research under review represents one of the categories of research permissible under 45 CFR 46.306(a)(2);

2) any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

3) the risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;

4) procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;

5) the information is presented in language which is understandable to the subject population;

6) adequate assurance exists that parole boards will not take into account a prisoner’s participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

7) where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or
care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

Four categories of research involving prisoners are permitted under the federal regulations. They are:

1) studies of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

2) studies of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

3) research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere); and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults; or

4) research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject.

The Informed Consent Document must include additional information for potential subjects regarding the fact that participation or non-participation will have no effect on the duration of incarceration or terms of parole. Suggested language is in the Appendix of the Informed Consent Document template.

C. Children

Categories of Research Involving Children

Federal regulations permit IRBs to approve a research project involving children after determining which of the following categories applies, and only if the project satisfies all of the conditions in the applicable category [45 CFR 46, Subpart D (DHHS) and 21 CFR 50 Subpart D (FDA)]:

1) Research that does not involve greater than minimal risk may be approved if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians. The IRB may determine that permission of one parent or guardian is sufficient.

2) Research involving greater than minimal risk, but presenting the prospect of direct benefit to an individual subject, or a monitoring procedure that is likely to contribute to the subject's well-being, may be approved if the IRB finds that:
   • the risk is justified by the anticipated benefit to the subject;
   • the relationship of anticipated benefit to risk is at least as favorable as that presented by available alternative approaches; and
   • adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

The IRB may determine that permission of one parent or guardian is sufficient.

3) Research involving greater than minimal risk with no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition, may be approved if the IRB finds that:
   • the risk represents a minor increase over minimal risk;
• the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
• the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the subject's disorder or condition; and
• adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.

In compliance with federal regulations, the IRB must determine that permission of both parents is required, unless one parent is deceased, unknown, incompetent, or not reasonably available, or unless only one parent has legal responsibility for the care and custody of the child.

The regulations also indicate that children who are wards of the state, or any other agency, institution, or entity can only be included in research in this category if the research is related to their status as wards or conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards. If one of these criteria is met and the research is approved, the IRB must require appointment of an advocate for each child who is a ward in addition to the person acting as guardian or in loco parentis. One person may serve as the advocate for multiple wards, however this advocate must have the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child’s participation in the research and cannot be associated in any way (except as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

4) Research that is not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children may be approved if the IRB and the Secretary of DHHS, after consultation with a panel of experts in pertinent disciplines and following an opportunity for public review and comment, find that:
• the research in fact satisfies one of the above three conditions; or
• the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
• the research will be conducted in accordance with sound ethical principles; and
• adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.

In compliance with federal regulations, the IRB must determine that permission of both parents is required, unless one parent is deceased, unknown, incompetent, or not reasonably available, or unless only one parent has legal responsibility for the care and custody of the child.

The regulations also indicate that children who are wards of the state, or any other agency, institution, or entity can only be included in research in this category if the research is related to their status as wards or conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards. If one of these criteria is met and the research is approved, the IRB must require appointment of an advocate for each child who is a ward in addition to the person acting as guardian or in loco parentis. One person may serve as the advocate for multiple wards, however this advocate must have the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child’s participation in the research and cannot be associated in any way (except as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.
Assent

When children are involved in research, the IRB may require the assent (knowledgeable agreement) of the child, in addition to the permission of the parent(s). (See also Chapter 5, Section A, Informed Consent and Related Issues, for more information about assent.) Children should be asked whether or not they wish to participate in the research. The IRB determines whether all or some of the children are capable of assenting and determine how the assent is to be obtained and documented.

The regulations do not specify a certain age at which assent must be sought, but for most studies, the IRB suggests obtaining assent beginning at about age seven. In certain studies involving treatment for an illness or condition that is available only in the context of research study, the IRB may determine that the assent of the child is not necessary.

The IRB must determine and document whether assent is required of all children in the research, some of the children in the research or that assent is not required of any of the children in the research.

D. Cognitively Impaired Persons

NOTES:
- See Chapter 5, Section A, Informed Consent and Related Issues, for more information about who may provide consent on behalf of an incompetent adult.
- A commonly used questionnaire, the Evaluation to Sign Consent, which is posted on the "Forms/Templates" pages of the HSO web site, may be used to assess an individual's capacity to provide consent -- see below for more details.

Individuals in a wide variety of situations may have impaired decision-making capacity. For example, impairment may occur at times of great stress. Impaired capacity is not limited to individuals with neurologic, psychiatric, or substance abuse problems; conversely, individuals with neurologic, psychiatric, or substance abuse problems should not be presumed to be decisionally impaired. Some research questions may be answered only by research that involves persons with impaired decision making capacity; precluding this research would contribute to needless suffering. The most severely impaired individuals have the greatest need for the benefits of research on etiology and treatment. While this area is controversial, limiting research to the least impaired individuals would hamper research on the underlying causes and potential therapies of many disorders. Not all research will directly benefit the individual participant but may offer future benefits to others who have or will develop the condition or disorder. For example, genetic studies, biochemical measures, or other non therapeutic approaches may benefit subsequent generations.

Unlike research involving children, prisoners, pregnant women, and fetuses, no additional Department of Health and Human Services (DHHS) regulations specifically govern research involving persons who are cognitively impaired. While limited decision-making capacity should not prevent participation in research, it is important to keep in mind that additional scrutiny is warranted for research involving this population.
The NIH offers the following Points to Consider to assist IRBs and clinical investigators in their effort to protect participants in research who are, or may be, or may become decisionally impaired:

**Conflicting Roles and Potential Conflicts of Interest**
Potential and actual research participants, especially those with permanent or transient cognitive impairments, may find it difficult to understand the difference between research and treatment, and to understand researchers' multiple roles, making "therapeutic misconceptions" particularly problematic, and possibly creating confusion among participants and their families. It is essential that the consent process (including consent documents) clearly indicate differences both between individualized treatment and research and between clinician and clinical investigator.

**Assessing Capacity to Consent**
Individual's capacities, impairments, and needs must be taken into account in order to develop practical and ethical approaches to enable them to participate in research. A clear understanding of the implications of various cognitive impairments, along with a careful consideration of proposed clinical research methodology, is required. Assessment is complex; simply answering a certain number of factual questions about a protocol may not be an adequate assessment. A key factor in participants' decision making is their appreciation of how the risks, benefits, and alternatives to participation in the study apply to them personally.

Limited decision making capacity covers a broad spectrum. A healthy person in shock may be temporarily decisionally impaired. Another may have been severely mentally retarded since birth, while yet a third who has schizophrenia may have fluctuating capacity. Researchers should be sensitive to the differing levels of capacity and use assessment methods tailored to the specific situation. Further, researchers should carefully consider the timing of assessment to avoid periods of heightened vulnerability when individuals may not be able to provide valid informed consent.

Both IRBs and clinical investigators must keep in mind that decision making capacity may fluctuate, requiring ongoing assessment during the course of the research. The consent process should be ongoing. The IRB, at its discretion, may require an outside witness to observe the consent process.

Because no generally accepted criteria for determining competence to consent to research exists for persons whose mental status is uncertain or fluctuating, the role of the IRB in assessing the criteria proposed by the investigator is of major importance. The selection of an appropriate representative to consent on behalf of those unable to consent for themselves must be accomplished without clear guidance from statutes, case law, or regulations.

**Comprehension**
The determination of a subject's ability to understand the implications of the decision to participate in research is best made by the clinician/investigator. In most cases, it will be the clinician/investigator who is in the ideal position to evaluate the subject's ability to understand the implications of the research and whether the subject is making a rational decision to participate. Likewise, in most studies it is the clinician/investigator who can best make a judgment of the subject's ability to understand and follow the protocol.

In developing the consenting process, the investigator is obligated to incorporate any special accommodations necessary to assure that the subject population or their surrogates comprehend the nature and purpose of the study. Useful techniques may include simplified consent documents, supplemental summary sheets, formal Q&A sessions for the subject and family or friends, and waiting periods after the initial discussion before the prospective subject actually enrolls.
There is no universally accepted test or standard for making a determination of comprehension. This process should operate in research studies in much the same manner as the informed consent process in clinical treatment that does not involve research.


Voluntary Agreement
Closely related to the determination of the ability to comprehend the nature of the study is the importance of ensuring that subjects' participation is completely voluntary. Some knowledge and assessment of the subject's competence is relevant to a determination of whether voluntary participation is evidenced by a written consent, or in the case of persons lacking legal capacity to consent, their assent. Research should not be conducted against the wishes of the subject, and making certain that the written documents are indeed a reflection of reality is the function of the individual researcher and the IRB.

Second Signature on the Consent Document
There are many situations in which a subject should be encouraged to authorize the involvement of family members. However, the permission of another party will be required only when the subject is determined to lack the legal ability to provide an informed consent. This would include children (when research is conducted in the state of Iowa, unmarried persons under the age of 18) and persons adjudicated incompetent. This also includes persons who are not capable of understanding the nature of their illness or the risks, benefits, and natural consequences of participation. Also see Chapter 5, Section A, Informed Consent and Related Issues, for more information about who may provide permission for an incompetent adult to participate in a research study.

In conclusion, in all human research, varied degrees of research risk and decisional impairment call for varied levels of scrutiny and safeguards; additional protections may be highly advisable in certain circumstances. But treating all individuals who have cognitive deficits as incapable of understanding research is inaccurate and disrespectful of their autonomy. Many individuals, adequately informed, may be willing to undertake certain risks so that they, or others, may benefit in the future. Researchers and IRBs must strive for a balance that maximizes potential benefits and opportunities, recognizes and extends individual autonomy, and minimizes risks associated with scientific inquiry.
Collaborative Research

UI IRBs may approve human subjects research activities at locations for which the IRB has an understanding of the local research context or the University is assured that there is appropriate oversight for the conduct of human subjects research. The UI IRBs approve collaborative projects within the UI and have mechanisms in place to assure appropriate oversight of collaborative research with non-UI entities.

1. With other UI Personnel

The UI encourages collaborative research projects across departments. Research team members can be from any department on the UI campus. There are some projects that may develop into the sharing of information with other researchers who are not members of the research team. Research team members should not share data or specimens with investigators outside of the research team for the project unless the subject is informed of this possibility in the informed consent document. Refer to the section on Data and/or Specimens below for more information.

2. With non-UI entities

In the conduct of cooperative research projects, each institution (entity) is responsible for safeguarding the rights and welfare of human subjects and for complying with any applicable regulations. Federal regulations from DHHS and FDA [45 CFR 46.114 & 21 CFR 56.114] allow for cooperative research projects which involve more than one institution (or entity). To avoid duplication of review efforts by IRBs, institutions can choose to conduct joint reviews, rely upon the review of another qualified IRB, or make other arrangements to establish oversight responsibilities.

Discussion of how to assure the rights and welfare of human subjects in research at each entity involved in the research usually begins with an evaluation of whether or not each entity is “engaged” in human subjects research. An entity becomes “engaged” in human subjects research when its employees or agents (agents include all individuals performing institutionally designated activities or exercising institutionally delegated authority or responsibility):

i) intervene or interact with living individuals for research purposes OR
ii) obtain individually identifiable private information for research purposes

An entity is automatically considered to be “engaged” in human subjects research whenever it receives a direct DHHS award to support such research. In these cases, the awardee institution bears ultimate responsibility for protecting human subjects under the award. OHRP has provided guidance (www.hhs.gov/ohrp/humansubjects/assurance/engage.htm) and examples for when institutions are considered to be “engaged” in research and examples of when institutions are NOT “engaged” in research. The UI IRB makes a determination about whether or not a cooperating outside institution is engaged in human subjects research. This determination is made by the appropriate UI IRB Chair based on the outside institution’s role and whether or not that role meets any of the criteria for “engaged in research” as defined in the guidance above. Any questions an IRB chair might have regarding making that determination are posed to OHRP by phone call or e-mail. Please call the HSO for more information if there is any question about the involvement of outside institutions in human subjects research.

Once the determination is made that the outside institution is engaged in human subjects research, the following are the UI IRB policies with regard to IRB oversight at those institutions.

1) When the outside institution is receiving federal funds through a subcontract with the UI, the UI Division of Sponsored Programs requires documentation that the outside institution holds an FWA through the subcontract process. If the outside institution does not hold its own FWA, the UI requires that they obtain one prior to finalization of the subcontract.
If this is the case, and the other institution obtains its own FWA, there are a few methods of IRB oversight that the UI IRB would consider acceptable based on the circumstances of the project and the role of the other institution. The UI IRB could either

- accept a concurrent review of the research project with the other institution’s own IRB, or
- be the IRB of record for the other institution. This agreement is formalized through the use of an IRB Authorization Agreement, or
- accept the other institution’s IRB as the IRB of record for the project. This would be in cases where the UI determines that the outside institution’s IRB review will provide more appropriate expertise, oversight, and/or knowledge of local context for the UI role in the study. This agreement is formalized using an IRB Authorization Agreement or other equivalent agreement. The outside IRB is then added to the UI FWA.

EXCEPTION: Under limited circumstances, when the UI is able to assure understanding of the local context in relation to the proposed research and has sufficient resources to provide appropriate oversight during the conduct of the research, the UI may choose to extend its FWA to cover the outside institution’s role in the individual project. This agreement is formalized using an Individual Investigator’s Agreement. There are two instances whereby this mechanism will NOT be allowed:

a. If the non-assured institution is the primary awardee for a DHHS-funded project OR
b. If the non-assured institution routinely engages in the conduct of human subjects research.

If either of the above conditions apply to the cooperating institution or investigator, the non-assured institution will be required to obtain its own OHRP-approved FWA.

2) When the outside institution is not receiving federal funding for the study through a subcontract with the UI, the UI IRB requires that the research be conducted under either the other institution’s IRB oversight or the UI IRB takes on oversight of the research. In the former instance, the IRB will require documentation that the outside IRB will provide this oversight. In the latter instance, this agreement is documented through a formal IRB Authorization Agreement.

The UI IRB will oversee research for an outside institution only when the UI IRB is able to assure understanding of local context in relation to the proposed research and has sufficient resources to provide appropriate oversight during the conduct of the research.

For each of these mechanisms of collaborative research oversight, you must have the approval of the designated IRB(s) of record PRIOR to conducting any research that involves human subjects. So, you must have the signed agreements and requirements finalized prior to the final approval of the project by the UI IRB and before you can conduct multi-institutional research projects that involve human subjects. The final determination to enter into any agreements described in this section is made by the UI Institutional Official.
For projects that involve international sites, please see the section below on International Research.
Conflict of Interest – Investigator

Conflict of interest in research involves situations in which an investigator or research team member or an investigator or research team member’s immediate family has a significant financial interest that may compromise, or have the appearance of compromising, professional judgment in the design, conduct, or reporting of research. "Significant financial interest" means a financial interest in a sponsor of research or sponsor's competitor, or intellectual property (patents, copyrights, or trade secrets) held by an investigator or research team member or the investigator or research team member's immediate family (spouse or domestic partner and dependent children) individually or in aggregate including:

1. Payments in excess of $10,000 including salary, consulting fees, royalty or licensing payments from intellectual property, honoraria and/or gifts received within the past 12 months or anticipated for the next 12 months (excluding salary and other payments received from the University);
2. Equity interest worth more than $10,000 or more than 5% of the business entity as determined by reference to its publicly listed price (excluding mutual funds);
3. Any equity interest if the value cannot be determined by reference to publicly listed prices (e.g., start-up companies);
4. A position as director, officer, partner, trustee, employee, or any other position of management; or
5. Patent rights or royalties from such rights whose value may be affected by the outcome of the research, including royalties under any royalty-sharing agreements involving the University.

Personal agreements between sponsors and investigators, IRB members, or their immediate family members where the amount of compensation (consulting, board honoraria, or any other kind) could change depending on the outcome of a study or any other activity the faculty/IRB member performs as part of their University service are prohibited. In some cases, such arrangements are illegal under state law.

In the HawkIRB electronic application, you will be asked to state, for each member of your research team, if s/he has a significant financial interest in the project. An investigator will not be allowed by the HawkIRB system to submit the project for review unless this question is answered for each member of the research team. Once the project is submitted to the HSO, if any of the responses are “yes,” an automatic notification is sent by the HawkIRB system to a representative of the Conflict of Interest in Research Committee (CIRC). Any UI investigator holding a significant financial interest as defined above must disclose this interest in writing prior to submission of a grant or contract application or, for non-sponsored research, prior to initiation of the activity. The IRB will not review a study until the any conflicts of interest have been managed, and the research may not begin until the University has reviewed the disclosure and all parties have agreed to any necessary management strategies. If a new significant financial interest is created or if a new investigator with a significant financial interest is hired to work on the research project, that interest must be disclosed within 60 days.

More information on the UI conflict of interest policies can be found on the website of the Office of the Vice President for Research.
Course-Related Student Projects

All research meeting the definitions of human subjects research that is carried out at the University of Iowa or under its auspices must be reviewed and approved by an Institutional Review Board (IRB) prior to the start of the research. Accordingly, honors theses, research practica, and Master's or Doctoral theses involving human subjects must be submitted for IRB review.

The University recognizes that some student projects conducted to fulfill course requirements involve activities that, in a different context, might be viewed as research. As a general rule, when those activities are conducted solely to fulfill a course requirement, an element of the definition of research (the intent to develop or contribute to generalizable knowledge) is lacking. However, it is also the case that some classroom assignments could place people at risk.

The University of Iowa has determined that some classroom assignments may require review by the appropriate IRB. The University considers classroom assignments to be educational in nature, and not subject to IRB review, when all of the following criteria are true.

If any one of these criteria is not true, or if the project extends beyond these limitations, then the project must be sent to the appropriate IRB for review or a determination that an activity is not human subjects research.

1. The classroom assignment or activity is not designed to develop or contribute to generalizable knowledge. The only purpose of the assignment or activity is to teach research methodology.
2. The results of the assignment do not develop or contribute to generalizable knowledge because either:
   a) The results of the project do not at any time leave the classroom, or,
   b) The project involves gathering data from or about a company, agency, or organization and the data/results are shared only with that company, agency, or organization to be used internally for internal quality assurance or quality improvement purposes).
3. The project is limited to surveys/questionnaires/interview procedures, observation of public behavior, or standard educational exercises directly related to the topic(s) being studied in an official University course.
4. Surveys/questionnaires/interviews, if used, contain no sensitive personal questions (e.g., no questions about alcohol/drug use, sexual behavior/attitudes, criminal activity, medical history, grades/test scores) or other personal information that could "label" or "stigmatize" an individual.
5. The project does not include a special population that requires extra protections (pregnant women, prisoners, children, cognitively impaired individuals).
6. EITHER - information is recorded without any direct or indirect (code number) identifier linking anyone to his/her data - OR - if a direct or indirect identifier is used when recording the data, then the questions being asked could not reasonably harm a person's reputation, employability, financial standing, or place a person at risk of criminal or civil liability.
7. No University of Iowa faculty, staff or student is receiving monetary compensation or any type of support from an external company/organization/agency for collecting, analyzing or reporting the results of this project is not conducted on VA premises and does not use VA resources, and is not otherwise subject to oversight by a federal regulatory body.

Faculty Responsibilities

It is the responsibility of faculty to determine whether an assigned project involving humans can be classified as a course-related student project under the 7 criteria above. Faculty should contact the Human Subjects Office if assistance in making this determination is needed. It is the responsibility of faculty to discuss general principles of ethics with the class prior to the initiation of the project.
Disclosure

All surveys/questionnaires/interviews should be preceded by a disclosure of the following points to the respondent. If an information sheet is used, consider including these points in that document.

1. The student identifies him/herself as UI student who is performing the activity to fulfill a course requirement, and the course is specifically identified.
2. The name of the supervising faculty member to contact for questions is provided.
3. The persons who have access to the individual data and/or summarized results are specified (e.g., instructor only, company/organization/agency).
4. Respondents are informed that their participation is completely voluntary.
Data and/or Specimens
Most research involves the collection of data and/or specimens. This section outlines some issues with regards to data and/or specimen collection.

Existing Data or Specimens
Case Reports
Case reports (i.e. write-up of a single patient case) do not need prospective review by the IRB. Publishing a case report does not meet the federal regulatory definition of “human subjects research.” The IRB will review and provide approval for case reports when they are being submitted to a journal that requires IRB approval as a condition of publication – this is the journal’s requirement and not an IRB requirement.

Chart/Record Reviews
A human subject is defined, in part, as a living individual about whom an investigator conducting research obtains identifiable private information. Therefore, medical chart or other kinds of record review research (e.g., student records) require IRB review and approval. The IRB chair may authorize a waiver of informed consent for chart/record review research studies if the study is minimal risk, the rights and welfare of the subjects are not adversely affected, the research could not practically be carried out without the waiver, and, when appropriate, subjects are provided with pertinent information after participation.

Generally, a waiver of consent is granted when all of the chart/record information that will be used in the research study exists in the original records prior to the date of the IRB application -- such studies are considered retrospective chart/record reviews. However, if some or all of the information that will be used in the research will be taken from charts/records dated some time in the future (i.e., after the date of the IRB application), then consent from some or all subjects may be required.

In order to assist the IRB in making the determination for waiver of consent, the investigator should provide the inclusive dates of chart/record information that will be used in the study. In addition to describing the purpose or hypothesis being studied, and the types of analyses that will be done, the investigator should provide the IRB a list of specific variables that will be used from the original source. This could be done in the application itself, or by including the data collection forms that will be used for compiling the chart/record data.

If the research study involves gathering data from the UIHC medical record, the UIHC Joint Office for Compliance requires that a “Request for Information” form be completed and signed. The IRB ID number and date of IRB approval for the project in which the data will be used must be included. The UIHC Medical Record Data Request form is available on the IRB-01 Forms/Templates page.

Existing Specimens
Research involving existing specimens (e.g., all specimens are "on the shelf" at the time the application for IRB review is submitted) may be classified as exempt only if there is no link, either in the investigator's records or elsewhere (e.g., pathology department), linking the specimen back to the identity of the subject. Even though it may be difficult or time-consuming to determine the subject's identity, if there is a link, the research cannot be classified as exempt, but may be eligible for a classification of expedited research.

Research involving specimens, all of which have already been obtained at the time of the IRB application, may be eligible for a waiver of consent. For further information regarding a waiver of consent, please see Chapter 5 of this Guide.
Secondary Analysis of Existing Data

Any research that involves secondary use of data where individual subject records that include private identifiable information requires IRB review. For example, an investigator who plans to analyze an existing data set obtained from another source that includes private identifiable information should submit an application for IRB review if the data set contains records on individual human subjects. If the data set contains no identifiers (either direct or linked code numbers), and the results will not be submitted to the FDA, the project is not human subjects research. Otherwise, the project may be eligible for expedited review. If you have questions about whether or not your project requires IRB review, please contact the Human Subjects Office at (319) 335-6564 or by email at irb@uiowa.edu.

The IRB chair may waive informed consent if research is minimal risk, the rights and welfare of the subjects are not adversely affected, the research could not practicably be carried out without the waiver, and, when appropriate, subjects are provided with pertinent information after participation. Secondary analysis of already aggregated data sets (e.g., meta analysis) does not require IRB review, since the investigator does not obtain individual human subject information.

Prospectively Collected Data or Specimens

Specimens

If the study involves the collection of extra tissue or specimens beyond what is needed for a clinical procedure, IRB review and approval and an Informed Consent Document is required. In such cases, the subject should be informed as to the purpose for obtaining the specimen. If the specimen is going to be retained for future use beyond the purpose of the study for which it was obtained, the subject should be informed regarding who might have future access, for what purposes the specimen might be used, how to request destruction or removal of the specimen from future research use, whether there are plans to compensate the subject should a product be developed. The Informed Consent Document template contains suggested language addressing these issues.

Specimens (e.g., blood, tissue, other bodily fluids) collected as part of standard clinical procedures that are unused at the completion of the diagnostic or treatment process and are destined for disposal are often referred to as discarded specimens. The UIHC surgical consent form notifies patients that such materials may be discarded or used in research. However, the purpose of the UIHC surgical consent form is for a patient to consent to a surgical procedure. It is not intended for or adequate as an Informed Consent Document to participate in research. Therefore, studies involving discarded specimens obtained prospectively may require an Informed Consent Document. As a general rule, if the study requires obtaining other identifiable information about the patient (demographic, diagnostic) for use in the analysis, consent may be required. The chair may consider waiving informed consent only if the requirements for waiving informed consent are met.

Data Registry

A research registry is defined as the collection and maintenance of data in which:

1. the individuals in the registry have a common condition,
2. the individuals in the registry may be contacted for future studies, and
3. the names/data of the individuals may be used by investigators other than the original research team.

If a registry is being created, the investigator should include the name of the registry, the method of data storage, how subjects are informed of their inclusion in the registry, and how subject identity and information is protected in the New Project Application. The Informed Consent Document should inform a potential subject that if s/he decides to participate, his/her name will be
stored in a registry and s/he may be contacted in the future by investigators other than the current research team.

Not all compilations of individuals' names and associated data constitute a research registry. A database is not necessarily a registry. The key element in a registry is that names and other identifying information are being stored so that people other than the original research team may access the registry information in the future to contact individuals for other studies. For further guidance, please contact the Human Subjects Office.

Specimen/Data Repositories

If a University of Iowa researcher stores human specimens for the specific purpose of providing specimens and/or associated data to others who are not members of the original "specimen collection" research team, the IRB may require that the researcher provide additional information to the IRB for establishing a formal repository. The IRB has developed these special procedures based on guidance from the Office for Human Research Protections in the Department of Health and Human Services.

Purpose for Establishing a Formal Repository:

• to give the “collector investigator” authority and responsibility for distributing specimens or data from the repository if certain pre-determined guidelines are met
• to minimize the paperwork burden on “recipient investigators” (those individuals with whom the PI intends to share the specimens or data)

Features of a Formalized Repository:

• Repository PI (“collector”) obtains IRB approval for establishing and maintaining the repository
• Repository PI determines the conditions under which s/he will share specimens or data from the repository with Recipient Investigators
• Repository PI develops a “Usage Agreement” that describes those conditions
• Repository PI is responsible for maintaining a copy of the signed Usage Agreements

If Recipient Investigator agrees to those conditions, and the Repository PI and Recipient Investigator both sign the Usage Agreement, the Recipient Investigator does NOT need IRB approval – the Repository PI may provide the specimens or data based on the signed Usage Agreement alone

The Recipient Investigator DOES need IRB approval in the following circumstances:

a) If the Recipient Investigator wants to use the specimens or data in a manner that goes beyond what is described in the Usage Agreement (e.g., get subject identifiers so that additional data items can be obtained from medical records), the Recipient Investigator must submit an IRB application for review and approval. The IRB application should specifically describe why the Recipient Investigator cannot do his/her study without going beyond the terms of use in the Usage Agreement.

b) If the Recipient Investigator is being funded by a funding source that requires evidence of IRB approval (e.g., NIH), the Recipient Investigator should submit an IRB application for review and approval. The Recipient Investigator should include with his/her IRB application a copy of the funding agency grant, and a copy of the signed Usage Agreement so that the IRB knows that the terms of the Usage Agreement will be followed. IRB approval of the Recipient’s use of the specimens or data will be classified as exempt from the federal regulations. The funding agency will be notified by the Division of Sponsored Programs (via the DHHS 310 form) that the PI has obtained IRB approval for
an exempt project, and the PI will not have to submit continuing review applications for the duration of that grant.

Further information about establishing a formal specimen repository, along with sample usage agreements and additional information required by the IRB, may be found in a document called "Specimen/Data Repository Procedures at UI" on the IRB Policies and Guidance page. Investigators are encouraged to contact the Human Subjects Office for assistance before submitting an application to establish a formal registry.
Emergency Settings: Research in the Emergency Setting (Planned Emergency Research)

The federal regulations for the protection of human subjects in research require informed consent, with a few narrow exceptions. FDA regulations in 21 CFR 50.24 provides a narrow exception to the requirement for informed consent from each human subject, or his or her legally authorized representative, prior to initiation of an experimental intervention. The Department of Health and Human Services (DHHS) also outlines waiver criteria for DHHS funded research at [61 FR 51531]. These documents establish a single standard for this class of research.

The exception to the requirement for informed consent would apply to a limited class of research activities involving human subjects who are in need of emergency medical intervention but who cannot give informed consent because of their life-threatening medical condition, and who do not have a legally authorized person to represent them. The intent of the new regulation is to allow research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent, while establishing additional protections to provide for safe and ethical studies.

Persons with life-threatening conditions who can neither give informed consent nor refuse enrollment are a vulnerable population. FDA recognizes that the lack of autonomy and inability of subjects to give informed consent requires additional protective procedures in the review, approval, and operation of this research. The exception from the informed consent requirement permitted by the rule is conditional upon documented findings by the IRB. Because these projects almost certainly represent situations of more than minimal risk and certain requirements are necessary to conduct this research at the UI, call the HSO for guidance if you receive funding to conduct this type of research project.
Emergency Use of an Investigational Drug or Device


*FDA defines that emergency use means the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval. [21 CFR 56.102(d)]*

Obtaining an Emergency IND

The emergency use of an unapproved investigational drug or biologic requires an IND. If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND.

The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means.

Exemption from Prospective IRB Approval

Emergency use is defined as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)]. The emergency use provision in the FDA regulations [21 CFR 56.104(c)] is an exemption from prior review and approval by the IRB. The exemption, which may not be used unless the subject is in a life-threatening or severely debilitating situation in which no standard acceptable treatment is available, allows for one emergency use of a test article without prospective IRB review. Life-threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible. Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Not all emergency use requires an exemption from prospective IRB review. When there is time for prospective IRB approval, the University of Iowa IRB expects the investigator to complete a New Project application describing the emergency use. The application will be scheduled for review at the next IRB meeting (IRB-01 meets every week). The FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. [21 CFR 56.104(c)] Therefore, if the first use does not have prospective review, the IRB notifies the investigator that if it is possible subsequent use of the agent will occur, a New Project application should be submitted for IRB review immediately following the first emergency use. The FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

The investigator should notify the IRB-01 chair prior to the emergency use, however, this notification should not be construed as IRB approval. The investigator is required to file a written report within five working days, and notifying the chair is used to initiate tracking to ensure that the investigator files this report as required by [21 CFR 56.104(c)]. The FDA regulations do not provide for expedited IRB approval in emergency situations. An IRB must either convene and give "full board" approval of the emergency use or, if the conditions of [21 CFR 56.102(d)] are met and it...
is not possible to convene a quorum within the time available, the use may proceed without any IRB approval.

Some manufacturers will agree to allow the use of the test article, but their policy requires "an IRB approval letter" before the test article will be shipped. If it is not possible to convene a quorum of the IRB within the time available, the IRB-01 chair will send the sponsor a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). Although this is not an "IRB approval," the acknowledgment letter has been acceptable to manufacturers and has allowed the shipment to proceed.

**Exception From Informed Consent Requirement**

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

1. The subject is confronted by a life-threatening situation necessitating the use of the test article.
2. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
3. Time is not sufficient to obtain consent from the subject's legal representative.
4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within five working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB within 5 working days after the use of the test article.
Genetic Research

DNA projects, by nature of their subject matter, are reviewed for the following information in addition to the standard required review. Genetic information is uniquely personal information and has the potential to influence employment, insurance, finance, education and possibly self perception. Therefore, genetic information must be carefully maintained in order to protect against stigmatization, discrimination, or significant psychological harm to the subject.

IRB review considers the following issues in both the application and the Informed Consent Document, as applicable:

* Information that can be obtained from DNA samples in general, and the specific questions to be addressed in this study.
* The extent of subject and sample confidentiality if the sample and subsequent information will be part of a registry or database.
* The rights and limitations of subjects to require destruction of their sample and/or associated data at a future date. The rights and limitations of subjects to require that their sample and or associated data be stripped of any identifying information.
* Identifying information available to other researchers if their sample and/or associated data are part of a registry or database.
* Mechanisms for maintaining confidentiality in long-term studies, registries, or databases.
* Potential for commercial profit by the institution, investigator or sponsor from information gathered in this study.
* The availability or access to genetic counseling in cases where a study may reveal genetically important information (i.e., possessing genetic defects which could be passed on).
* Subjects must have the right to decline receiving genetic information.

In the absence of a specific authorization to maintain a DNA sample, DNA samples collected and stored or analyzed in connection with a research project shall be destroyed upon completion of the project or withdrawal of the individual from the project. This information must be clearly stated in the Informed Consent Document.

Before involving children in DNA research, the parent(s) or legal guardian(s) must review and sign the Informed Consent Document. The Informed Consent Document must give parents/guardians the option of whether or not they want the results (if available) of the genetic analysis disclosed to them. Whenever appropriate, the child's assent should be solicited. Upon reaching the age of majority, if the subject may request his or her information be disclosed that should be included in the Consent Document. Investigators must follow the appropriate measures with regard to releasing such information (e.g., counseling, etc.). In some cases it may be possible to determine that some members of the family are not genetic relatives. Issues of genetic relationships (paternity or maternity, as could be hidden by adoption or donor fertilization) and other incidental information should not be revealed. The standard Informed Consent Document template contains suggested language for genetic research and for storing tissue or specimens for future use.
HIPAA

The Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA) became effective on 4/14/2003. The Privacy Rule provides standards for maintaining the privacy of individually identifiable health information. It applies only to individually identifiable health information that is maintained by a covered entity. If the health information is individually identifiable and if it is held by a covered entity, it is likely to be considered “protected health information.”

**What is a covered entity?**
A covered entity is any of the following:
- a) a health plan,
- b) a health care clearinghouse (billing service), or
- c) a health care provider that transmits health information electronically.

**What is “protected health information” or PHI?**
PHI is health information that:
- a) is transmitted or maintained in any form (electronic, oral, paper) by a covered entity AND
- b) identifies the individual or could reasonably be used to identify the individual AND
- c) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual.

**What kinds of information could identify or reasonably identify the individual?**
Any of the following information for the individual, relative, employer, or household member of the individual are examples:
- Name, street address, city, county, precinct, zip code, geocodes smaller than state
- Date of birth, ages > 89 years of age, or other dates such as diagnosis dates, procedure dates, admission or discharge dates
- Telephone numbers, Fax numbers, E-mail addresses, Social Security number, Medical record number
- Health plan beneficiary numbers, Account numbers, Certificate/license numbers
- Vehicle identifiers and serial numbers or license numbers, Device identifiers and serial numbers
- Web URLs, Internet Protocol (IP) address numbers, Biometric identifiers including finger/voice prints
- Full face photographic images and any comparable images

**Is the University of Iowa a covered entity?**
No. The University of Iowa is considered a “hybrid entity” in the world of HIPAA. This is because the UI is a single legal component with both covered (e.g. UI Health Care, student health, College of Dentistry) and non-covered functions (e.g. Lipid Research Center, College of Law, etc.). The hybrid entity designation limits the HIPAA liability for the institution. The covered components may use or disclose PHI for treatment, payment, or operations. Research is not treatment, payment or operations so the covered components may not use or disclose PHI for research *except as permitted* in the regulations.

**What research use of PHI do the regulations permit?**
The regulations permit the use of PHI for research under two conditions: 1) you obtain a signed authorization from the patient, or 2) you receive a waiver of authorization from the IRB. At the University of Iowa, the authorization to use PHI is combined with the research informed consent document. Refer to the informed consent document template in the section called “Will My Health Information be Used During this Study?” for the authorization language. If you plan to look at, use, or create PHI for research purposes, a signed informed consent document that includes the “HIPAA” section authorizes the covered entity to disclose the PHI to the research team.

The waiver of authorization to use PHI for research purposes is separate from the waiver of elements of consent from 45CFR46. Like the DHHS waiver, the waiver of authorization to use PHI for research must be approved by the IRB or privacy board. Examples of research that might be eligible for a waiver include retrospective chart reviews or retrospective specimen studies. The New Project Application in HawkIRB includes questions to help the IRB decide whether or not the criteria for a waiver have been met for a given research project. These criteria include:

- The research could not **practically** be conducted without the waiver AND
- The research could not **practically** be conducted without access to and use of the PHI.
- The use or disclosure of the PHI involves no more than minimal risk to the privacy of individuals based on, at least, the presence of the following elements:
  a. The PI has an adequate plan to protect identifiers from improper use/disclosure
  b. The PI has an adequate plan to destroy identifiers at the earliest opportunity
  c. The PI give adequate written assurance that the PHI will not be disclosed to others.

**Examples of times you might look at, use, or create PHI for research purposes:**

- Look at a clinic schedule, a medical chart, or an electronic record, to schedule subjects for a study visit or identify a diagnosis for subjects, OR
- Conduct research with an inpatient population, OR
- Conduct medical testing, OR
- Conduct research on the GCRC, OR
- Conduct a retrospective or prospective chart review, OR
- Create or add information to an in-house database or registry for research use, OR
- Provide treatment through a research protocol, OR
- Collect medical records from an outside institution, OR
- Look at or use data from a QA/QI database, OR
- Compare information collected on a survey to information in the medical record then YOU are looking at, using or creating PHI for research purposes!

For more information about the HIPAA Privacy Rule, check out the HIPAA page on the HSO website.

At the **UI:**
- UIHC HIPAA website
- University of Iowa HIPAA website

**Federal links:**
- HIPAA Privacy Rule Office of Civil Rights
- NIH Information for Researchers on the HIPAA Privacy Rule
- Privacy Rule Complete Regulation Text (45CFR 160 and 164, unofficial text)
- Privacy Rule Summary
International Research

Procedures normally followed outside the United States for research involving human subjects may differ from those set forth in federal and University policies. These may result from differences in language, cultural and social history, and social mores. In addition, national policies such as the availability of national health insurance, philosophically different legal systems, and social policies may make U.S. forms and procedures inappropriate. In federally funded research, research activities in a foreign country may be approved if the procedures proscribed by a foreign institution are equivalent to those in the U.S. OHRP provides a listing of the laws, regulations, and guidelines that govern human subjects research in many countries around the world. A link to this listing is provided here.

Requests to review and waive some standard elements of domestic approvals may be considered. However, protections afforded subjects must approximate those provided to subjects in the United States. The investigator should call the Human Subjects Office or contact the Chair of the appropriate IRB to discuss these issues.
Investigational Drugs or Biologics

IND – Investigational New Drug

Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

During a new drug’s early preclinical development, the sponsor’s primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

FDA’s role in the development of a new drug begins when the drug’s sponsor (usually the manufacturer or potential marketer) having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.

There are three IND types:

- **An Investigator IND** is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.

- **Emergency Use IND** allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.

- **Treatment IND** is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

Once the IND is submitted to FDA, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk. For more information on IND’s, refer to the following link: [FDA (CDER) website](#). UI investigators conducting studies with an IND are required to submit documentation from the sponsor (either as a letter from the FDA or sponsor, email from the FDA or sponsor or indication on the commercial sponsor’s protocol) of the IND number assigned by the FDA. This documentation must be attached to the new project application in HawkIRB. IRB staff will check for this documentation and return protocols with inadequate documentation of the IND number.

Promotion and Charging for Investigational New Drugs

[Taken from 21 CFR 312.7]

**Promotion.** A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context (e.g. in advertisements, brochures or any recruitment media) that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including the dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or
effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

A sponsor or investigator shall not commercially distribute or test market an investigational new drug. In addition, a investigator should be aware that a sponsor cannot undoably prolong an investigation after finding that the results of the investigation appear to establish sufficient data to support a marketing application.

**Charging.** Charging for an investigational drug in a clinical trial under an IND is NOT permitted without the prior written approval of FDA. In requesting such approval, the sponsor shall provide a full written explanation of why charging is necessary in order for the sponsor to undertake or continue the clinical trial, e.g., why distribution of the drug to test subjects should not be considered by the sponsor to be part of the normal cost of doing business.

Investigators should include in the “Costs” section of the Informed Consent Document a statement that there will be no charges for the investigational new drug(s) used in the study. If this statement is not included in the informed consent document, the UI IRB will only allow its absence if the investigator attaches the prior written approval of the FDA to the sponsor to allow for test subject charges. This authorization to charge for an investigational drug under this section may be withdrawn by FDA if the agency finds that the conditions underlying the authorization are no longer satisfied. In such instance, it is the responsibility of the investigator to submit a modification to the informed consent document inserting the required statement as indicated above. In such cases where charges are allowed, sponsors are not allowed to commercialize the investigational new drug by charging a price larger than that necessary to recover costs of manufacture, research, development, and handling of the investigational drug. The investigator must be cognizant of this rule when participating in a clinical trial of an investigational new drug.

**Treatment protocol or treatment IND.** A sponsor or investigator may charge for an investigational drug for a treatment used under a treatment protocol or treatment IND provided:

1. There is adequate enrollment in the ongoing clinical investigations under the authorized IND;
2. Charging does not constitute commercial marketing of a new drug for which a marketing application has not been approved;
3. The drug is not being commercially promoted or advertised; AND
4. The sponsor of the drug is actively pursuing marketing approval with due diligence.

FDA must be notified in writing in advance of commencing any such charges, in an information amendment. Authorization for charging goes into effect automatically 30 days after receipt by FDA of the information amendment, unless the sponsor is notified to the contrary.

**Investigational Use of FDA-approved Drugs or Biologics**

The investigational use of approved, marketed products differs from the situation described above. "Investigational use" suggests the use of an approved product in the context of a clinical study protocol [see 21 CFR 312.3(b)]. When the principal intent of the investigational use of a test article is to develop information about the product’s safety or efficacy, submission of an IND or IDE may be required. However, according to 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug or biologic does not require submission of an IND if all six of the following conditions are met:

(i) it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
(ii) it is not intended to support a significant change in the advertising for the product;
(iii) it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
(iv) it is conducted in compliance with the requirements for IRB review and informed consent;
(v) it is conducted in compliance with the requirements concerning the promotion and sale of drugs; and
(vi) it does not intend to invoke the exception for informed consent requirements [21 CFR 50.24].

Sponsor-Investigator (Investigator-Initiated) Research with Drugs or Biologics

The following information is intended to provide sponsor-investigators with information to guide them through the FDA requirements for sponsor-investigators who hold an IND. The federal regulations for INDs are found under 21 CFR 312. Responsibilities of sponsors and investigators are also contained in the International Conference on Harmonisation (ICH) Guidance for Industry, E6 Good Clinical Practice. For more information, review the FDA’s Center for Drug Evaluation and Research (CDER) web site www.fda.gov/cder.

This text is a synopsis of requirements specific to sponsor-investigators who hold INDs. It is intended to be a guide, but does not include the complete text of the regulations. Hyperlinks are included throughout the following text so that you may read the corresponding regulations. Sponsor-investigators must review and be familiar with the federal regulations before undertaking these responsibilities.

Sponsor-investigators are also required to follow all federal regulations and University of Iowa policies and guidance for Human Subjects research. University of Iowa policies and guidance for human subjects research are available in this Investigator’s Guide.

What is a Sponsor-Investigator?

When an Investigator holds an IND for the product being tested in a particular research study, he/she must also assume the role of the Sponsor, and is called a “Sponsor-Investigator.” The FDA defines a Sponsor-Investigator as “means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.” [21 CFR 312.3]

What must the Sponsor-Investigator report to the FDA?

Sponsor-investigators have extensive reporting requirements under FDA regulations.

1. New protocol 21 CFR 312.30a

   Once the IND has been approved by the FDA, the sponsor-investigator must submit a new protocol for any study not contained in the IND application. The protocol can be submitted before or after IRB approval. The study may not begin until the protocol has been reviewed by the FDA and approved by the IRB.

2. Changes in the protocol 21 CFR 312.30b

   The following protocol changes must be submitted to the FDA.
   • For Phase 1 studies, any change that significantly affects the safety of subjects.
   • For Phase 2 and 3 studies, any change that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study.
3. New investigator 21 CFR 312.30c
The addition of a new investigator must be reported to the FDA within 30 days of the investigator being added. The IND may not be shipped to the new investigator until the FDA has been notified.

4. Information amendments 21 CFR 312.31
Any essential information that is not included in a protocol amendment, IND safety report, or annual report must be submitted to the FDA. Examples of essential information include new toxicology, chemistry, or other technical information. Information amendments should be submitted as necessary, but not more than every 30 days.

5. IND safety/adverse events reports 21 CFR 312.32
An investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately. [21 CFR 312.64].
Guides to adverse event reporting are indicated below:
- **Unexpected fatal or life-threatening** experiences that are associated with the investigational drug must be reported to the FDA by fax or telephone as soon as possible, but no later than 7 days after the sponsor-investigator initially receives the information.
- **Serious and unexpected adverse events** associated with the use of the drug that are not fatal or life-threatening must be submitted to the FDA as soon as possible, but no later than 15 days after the sponsor-investigator initially receives the information.

6. Annual reports 21 CFR 312.33
The sponsor-investigator must submit a progress report to the FDA within 60 days of the anniversary date that the IND went into effect. The sponsor is also required under 21 CFR 312.33 to submit annual reports to the FDA on the progress of the clinical investigations. [21 CFR 312.64]. The expected contents of the progress report are included in 21 CFR 312.33.

7. Withdrawal of an IND 21 CFR 312.38
Sponsor-investigators must inform the FDA of desire to withdraw an IND.

8. Discontinuation of an investigation 21 CFR 312.31(a)2
If the sponsor-investigator determines that an investigation drug presents an unreasonable and significant risk to subjects, she/he must discontinue the investigation within 5 working days after determining that the investigation should be discontinued. A report of the discontinuation of the investigation should be submitted to the FDA within 5 working days of the discontinuance.

9. Financial disclosure reports 21 CFR 312.57d
Any changes to financial disclosure information must be promptly reported to the FDA during the investigation and for 1 year following completion of the study.

What records must a sponsor-investigator maintain?
The sponsor-investigator is responsible for maintaining the following records during and for 2 years after the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such an indication, the sponsor-investigator is responsible for maintaining the following records until 2 years after the investigation is discontinued and FDA is notified. [21 CFR 312.62]. The sponsor-investigator must make these available to FDA inspectors at their request.

1. Drug accountability 21 CFR 312.57a
   The sponsor-investigator must maintain records showing receipt, shipment, or other disposition of the investigational drug.

2. Financial interest 21 CFR 312.57b
   The sponsor-investigator must maintain records showing any financial interests of any of the clinical investigators involved in the study (see also 21 CFR 54). The clinical investigator shall provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements. The clinical investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study [21 CFR 312.64].

3. Case Histories 21 CFR 312.62b
   The sponsor-investigator must maintain accurate case histories that record all observations and other data pertinent to the investigation on each subject who received the investigational drug and each subject who was employed as a control in the investigation. [21 CFR 312.62]. Case histories include the case report forms and supporting data such as signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

4. Essential documents ICH E6 S8
   The sponsor-investigator must maintain documents included in ICH E6 S8. These documents are considered essential to conducting a clinical trial and are subject to audit by regulatory authorities. The investigator shall furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained. Examples of essential documents are signed protocol and amendments, informed consent documents, IRB approval notices, and signed, dated, and completed case report forms (CRFs). For a complete list of essential documents, see ICH E6 S8.

What are the sponsor-investigator's responsibilities as a sponsor?
The sponsor-investigator carries all responsibilities toward co-investigators that are normally assigned to the sponsor.

1. General responsibilities of sponsors 21 CFR 312.50
   The sponsor-investigator is responsible for
   • selecting qualified investigators and providing them with the information they need to conduct an investigation properly.
   • ensuring proper monitoring of the investigation. For more information on monitoring guidelines, see Section 5.18 of the ICH Guidance.
ensuring that the investigation is conducted in accordance with the general investigational plan and protocols contained in the IND.
maintaining an effective IND with respect to the investigations.
complying with FDA regulations with regard to the promotion and charging for investigational new drugs. See Chapter 9, Section IND – Investigational Drugs or Biologics, Sub-section Promotion and Charging for Investigational New Drugs above.
ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug.

2. Selection and monitoring of investigators 21 CFR 312.53 – 312.56
The sponsor-investigator is responsible for
• selecting qualified investigators and monitors.
• ensuring that the study drug is shipped only to participating investigators.
• informing co-investigators of new observations with regard to the investigational drug and progress of the study.
• reviewing on-going investigations, including assuring compliance of all investigators with the protocol, reviewing and evaluating safety and efficacy data of the investigational drug, and discontinuing studies that are deemed to pose an unreasonable and significant risk to subjects.

3. Recordkeeping and record retention 21 CFR 312.57
The sponsor-investigator is responsible for maintaining study records, as described above.

4. Inspection of sponsor’s records and reports 21 CFR 312.58
The sponsor-investigator must allow FDA employees access to all records and reports at their request. Drug Enforcement Administration and Department of Justice employees must be given access to records and reports involving controlled substances at their request.

5. Disposition of unused supply of investigational drug 21 CFR 312.59
If the investigation is terminated, suspended, discontinued, or completed, the sponsor-investigator is responsible for assuring that all co-investigators return any unused supplies of the investigational drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR 312.59 [21 CFR 312.62]. The sponsor-investigator must maintain records of the disposition of the drug as described above.

What are the sponsor-investigator’s responsibilities as an investigator?
As an investigator, the sponsor-investigator has all the responsibilities of investigators in any clinical trial.

1. General responsibilities of investigators 21 CFR 312.60
The sponsor-investigator is responsible for
• ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations.
• protecting the rights, safety, and welfare of subjects under the investigator’s care
• ensuring the control of drugs under investigation.
2. Control of the investigational drug 21 CFR 312.61
The sponsor-investigator must administer the investigational drug only to subjects under his/her direct supervision, or under the supervision of a sub-investigator responsible to the investigator. The sponsor-investigator must also ensure that the investigational drug is not given to any person not authorized to receive it.

3. Investigator recordkeeping and record retention 21 CFR 312.62
The sponsor-investigator is responsible for maintaining adequate records of the disposition of the drug, including dates, quantity, and use by subjects. This is described above.

4. Investigator reports 21 CFR 312.64
The sponsor-investigator must provide reports to the FDA as described above.

5. Assurance of IRB review 21 CFR 312.66
The sponsor-investigator is responsible for
- assuring that a qualified IRB will be responsible for initial and continuing review and approval of the investigation.
- providing a letter or email from the FDA (as an attachment to the HawkIRB new project application) giving the IND number assigned by the FDA.
- assuring that he/she will report to the IRB all changes and unanticipated problems involving risk to human subjects or others.
- assuring that he/she will not make any changes in the investigation without prior IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

6. Inspection of investigator’s records and reports 21 CFR 312.68
The sponsor-investigator must allow FDA employees access to all records and reports at their request. An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to 21 CFR 312.62 [21 CFR 312.68]. The investigator is not required to divulge participant names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

7. Handling of controlled substances 21 CFR 312.69
The sponsor-investigator must take adequate precautions to ensure the safe and secure handling of controlled substances. The investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.
Investigational Medical Devices
IDE – Investigational Device Exemption

An investigational device is a medical device which is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. Clinical investigations undertaken to develop safety and effectiveness data for medical devices must be conducted according to the requirements of the IDE regulations [21 CFR part 812]. An IDE study may not necessarily commence 30 days after an IDE submission to FDA. Certain clinical investigations of devices (e.g., certain studies of lawfully marketed devices) may be exempt from the IDE regulations [21 CFR 812.2(c)]. Unless exempt from the IDE regulations, an investigational device must be categorized as either "significant risk" (SR) or "nonsignificant risk" (NSR) – see the section below for more information. The determination that a device presents a nonsignificant or significant risk is initially made by the sponsor. The proposed study is then submitted either to FDA (for SR studies) or to an IRB (for NSR studies).

The IRB's SR/NSR determination has significant consequences for the study sponsor, FDA, and prospective research subjects. SR device studies must be conducted in accordance with the full IDE requirements [21 CFR part 812], and may not commence until 30 days following the sponsor's submission of an IDE application to FDA. Submission of the IDE application enables FDA to review information about the technical characteristics of the device, the results of any prior studies (laboratory, animal and human) involving the device, and the proposed study protocol and consent documents. Based upon the review of this information, FDA may impose restrictions on the study to ensure that risks to subjects are minimized and do not outweigh the anticipated benefits to the subjects and the importance of the knowledge to be gained. The study may not commence until FDA has approved the IDE application and the IRB has approved the study.

In contrast, NSR device studies do not require submission of an IDE application to FDA. Instead, the sponsor is required to conduct the study in accordance with the "abbreviated requirements" of the IDE regulations [21 CFR 812.2(b)]. Unless otherwise notified by FDA, an NSR study is considered to have an approved IDE if the sponsor fulfills the abbreviated requirements. The abbreviated requirements address, among other things, the requirements for IRB approval and informed consent, recordkeeping, labeling, promotion, and study monitoring. NSR studies may commence immediately following IRB approval.

Once the final SR/NSR decision has been rendered by the IRB (or FDA), the IRB must consider whether or not the study should be approved. In considering whether a study should be approved, the IRB should use the same criteria it would use in considering approval of any research involving an FDA regulated product [21 CFR 56.111]. FDA considers all SR studies to present more than minimal risk, and thus, full IRB review is necessary. In making its determination on approval, the IRB should consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures.

Significant and Nonsignificant Risk Medical Device Studies

The Investigational Device Exemption (IDE) regulations [21 CFR part 812] describe two types of device studies, "significant risk" (SR) and "nonsignificant risk" (NSR). An SR device study is defined [21 CFR 812.3(m)] as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and

1. is intended as an implant; or
2. is used in supporting or sustaining human life; or
3. is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or
4. otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
An NSR device investigation is one that does not meet the definition for a significant risk study. NSR device studies, however, should not be confused with the concept of "minimal risk," a term utilized in the Institutional Review Board (IRB) regulations [21 CFR part 56] to identify certain studies that may be approved through an "expedited review" procedure. For both SR and NSR device studies, IRB approval prior to conducting clinical trials and continuing review by the IRB are required. In addition, informed consent must be obtained for either type of study [21 CFR part 50].

**Distinguishing Between SR and NSR Device Studies**

The effect of the SR/NSR decision is very important to research sponsors and investigators. SR device studies are governed by the IDE regulations [21 CFR part 812]. NSR device studies have fewer regulatory controls than SR studies and are governed by the abbreviated requirements [21 CFR 812.2(b)]. The major differences are in the approval process and in the record keeping and reporting requirements. The SR/NSR decision is also important to FDA because the IRB serves, in a sense, as the Agency's surrogate with respect to review and approval of NSR studies. FDA is usually not apprised of the existence of approved NSR studies because sponsors and IRBs are not required to report NSR device study approvals to FDA. If an investigator or a sponsor proposes the initiation of a claimed NSR investigation to an IRB, and if the IRB agrees that the device study is NSR and approves the study, the investigation may begin at that institution immediately, without submission of an IDE application to FDA.

If an IRB believes that a device study is SR, the investigation may not begin until both the IRB and FDA approve the investigation. To help in the determination of the risk status of the device, IRBs should review information such as reports of prior investigations conducted with the device, the proposed investigational plan, a description of subject selection criteria, and monitoring procedures. The sponsor should provide the IRB with a risk assessment and the rationale used in making its risk determination.

**SR/NSR Studies and the IRB: The NSR/SR Decision**

The assessment of whether or not a device study presents a NSR is initially made by the sponsor. If the sponsor considers that a study is NSR, the sponsor provides the reviewing IRB an explanation of its determination and any other information that may assist the IRB in evaluating the risk of the study. The sponsor should provide the IRB with a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of patient selection criteria and monitoring procedures, as well as any other information that the IRB deems necessary to make its decision. The sponsor should inform the IRB whether other IRBs have reviewed the proposed study and what determination was made. The sponsor must inform the IRB of the Agency's assessment of the device's risk if such an assessment has been made. The IRB may also consult with FDA for its opinion.

The IRB may agree or disagree with the sponsor's initial NSR assessment. If the IRB agrees with the sponsor's initial NSR assessment and approves the study, the study may begin without submission of an IDE application to FDA. If the IRB disagrees, the sponsor should notify FDA that an SR determination has been made. The study can be conducted as an SR investigation following FDA approval of an IDE application.

If the sponsor has an IDE number or the IRB requires an IDE, the investigator must submit to the IRB documentation of the assignment of an IDE number using the HawkIRB system. This documentation can be an e-mail from the FDA or sponsor, letter from the FDA or sponsor, or indication on the commercial sponsor protocol that gives the IDE number as assigned by the FDA. IRB staff will check for this documentation and return protocols with inadequate documentation of the IDE number.
Investigator-Initiated Research with Medical Devices

The following information is intended to provide sponsor-investigators with information to guide them through the FDA requirements for sponsor-investigators who hold an IDE. The federal regulations for IDEs are found under 21 CFR 812. Responsibilities of sponsors and investigators are also contained in the International Conference on Harmonisation (ICH) Guidance for Industry, E6 Good Clinical Practice. For more information, review the FDA’s Center for Devices and Radiologic Health (CDRH) web site http://www.fda.gov/cdrh.

This is a synopsis of requirements specific to sponsor-investigators who hold IDEs. It is intended to be a guide, but does not include the complete text of the regulations. Hyperlinks are included throughout this document so that you may read the corresponding regulations. Sponsor-investigators must review and be familiar with the federal regulations before undertaking these responsibilities.

Sponsor-investigators are also required to follow all federal regulations and University of Iowa policies and guidance for Human Subjects research. University of Iowa policies and guidance for human subjects research are available in this Investigator’s Guide.

What is a Sponsor-Investigator?

When an Investigator holds an IDE for the product being tested in a particular research study, he/she must also assume the role of the Sponsor, and is called a “Sponsor-Investigator.” The FDA defines a Sponsor-Investigator as “an individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used . . . . The obligations of a sponsor-investigator under this part include those of an investigator and a sponsor.” [21 CFR 812.3]

What must the Sponsor-Investigator report to the FDA and/or IRB? 21 CFR 812.150(a)

Sponsor-investigators have extensive reporting requirements under FDA regulations.

1. Changes in the protocol 21 CFR 812.35

Changes to the investigational plan or manufacturing process must be submitted to the FDA for approval if they significantly affect the validity of study data, risk-benefit ratio, scientific soundness of the study, or the rights, safety, or welfare of subjects. These changes should be submitted to the FDA as a supplement to the IDE protocol and must be approved by the FDA before being implemented.

Changes that do not meet the above criteria (e.g., adding follow-up visits, changing secondary endpoints, etc.) should be submitted to the FDA within 5 working days of implementation of the change. Minor changes to the purpose of the study, risk analysis, monitoring procedures, labeling, informed consent materials, and IRB information that do not affect the validity of study data, risk-benefit ratio, scientific soundness of the study, or the rights, safety, or welfare of subjects can be submitted with the annual report.

An investigator shall notify the sponsor and the reviewing IRB (21 CFR 56.108(a) (3) and (4) of any deviation from the investigational plan to protect the life or physical well-being of a participant in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human participants, FDA and IRB in accordance with [21 CFR 812.35(a)]
For more information, see Changes or Modifications during the Conduct of a Clinical Investigation; Final Guidance for Industry and CDRH Staff

2. IDE safety/adverse device effects 21 CFR 812.150b
   The sponsor-investigator must report all unanticipated adverse device effects to the FDA and the IRB within 10 working days of receiving the first notice of the event.

   Click here for a decision tree to help determine when to report adverse events relating to investigator-held IDEs.

3. Withdrawal of IRB approval 21 CFR 812.150b
   The sponsor-investigator must inform the FDA, all reviewing IRBs, and participating investigators of withdrawal of approval of an investigation or any part of an investigation by any reviewing IRB. This notification must occur within 5 working days after receipt of the withdrawal of approval.

4. Withdrawal of FDA approval 21 CFR 812.150b
   The sponsor-investigator must notify all reviewing IRBs and participating investigators of any withdrawal of FDA approval. This notification must occur within 5 working days after receipt of the withdrawal of approval.

5. Current investigator list 21 CFR 812.150b
   The sponsor-investigator must provide the FDA with a current list of investigators participating in the investigation. This list must be provided to the FDA every 6 months.

6. Annual reports 21 CFR 812.150b
   The sponsor-investigator must submit a progress report to all reviewing IRBs at regular intervals, at least yearly. The first report must be within 60 days of the anniversary date that the IDE went into effect. For IDEs that have been determined to be significant risk, these reports must also be submitted to the FDA.

7. Recall and device disposition 21 CFR 812.150b
   The sponsor-investigator must notify the FDA and all reviewing IRBs of any request that an investigator return, repair, or otherwise dispose of any units of a device. The notification must occur within 30 working days after the request is made.

8. Discontinuation of an investigation 21 CFR 812.150b
   The sponsor-investigator must report the completion or termination of an investigation. These reports should be made by submitting a final report.
   For significant risk devices, the sponsor-investigator must notify the FDA within 30 working days and all reviewing IRBs within 6 months of the completion of the investigation.
   For non-significant risk devices, the sponsor must notify all reviewing IRBs within 6 months of completion of the study.

9. Informed consent 21 CFR 812.150b
   The sponsor-investigator must report to the FDA any use of the IDE without informed consent. This report must be submitted within 5 working days of receipt of notice of this use.

10. Significant risk device determinations 21 CFR 812.150b
    If an IRB determines that a device is significant risk, whereas the sponsor-investigator had
proposed it to be a non-significant risk device, the sponsor-investigator must notify the FDA of this decision within 5 working days after learning of the IRB’s determination.

In deciding whether or not a medical device is a significant risk, the IRB considers if the device:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a participant. \[21 \text{CFR } 812.3(m)(1)\].
- Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a participant. \[21 \text{CFR } 812.3(m)(2)\].
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a participant. \[21 \text{CFR } 812.3(m)(3)\].
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. \[21 \text{CFR } 812.3(m)(4)\].

11. Financial disclosure reports \[21 \text{CFR } 812.43\]
    A clinical investigator shall disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements. The investigator shall promptly update any changes to financial disclosure information and report it to the FDA during the investigation and for 1 year following completion of the study.

**What records must a sponsor-investigator maintain?**

The sponsor-investigator is responsible for maintaining the following records during and for 2 years after completion or termination of the investigation or 2 years after the records are no longer needed to support a premarket approval application or a notice of completion of a product development protocol. \[21 \text{CFR } 812.140d\]. The sponsor-investigator must make these available to FDA inspectors at their request.

1. **Correspondence** \[21 \text{CFR } 812.140\]
   The sponsor-investigator must maintain copies of all correspondence with other investigators, reviewing IRBs, monitors, and the FDA including required reports.

2. **Financial interest** \[21 \text{CFR } 812.140\]
   The sponsor-investigator must maintain records showing any financial interests of any of the clinical investigators involved in the study (see also \[21 \text{CFR } 54\]).

3. **Device records** \[21 \text{CFR } 812.140\]
   A participating investigator shall maintain the following accurate, complete and current records relating to the investigator’s participation in an investigation. The sponsor-investigator must maintain records relating to the shipment, receipt, use (including adverse effects), and disposition of the device.

   Additionally, for nonsignificant risk devices, the investigator must maintain
   - the name and intended use of the device (type and quantity of the device, the dates of its receipt, and the batch number or code mark).
   - a brief explanation of why the device is not a significant risk.
   - the name and address of each investigator and the names of all persons who received, used, or disposed of each device.
• why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of
• a statement of the extent to which Good Manufacturing Practice (GMP) regulations will be followed in manufacturing the device (see also 21 CFR 820).

4. Case Histories 21 CFR 812.140
The sponsor-investigator must maintain accurate case histories that record all observations and other data pertinent to the investigation on each subject exposed to the investigational device. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

5. Essential documents ICH E6 S8
The sponsor-investigator must maintain documents included in ICH E6 S8. These documents are considered essential to conducting a clinical trial and are subject to audit by regulatory authorities. Examples of essential documents are signed protocol and amendments, signed and dated informed consent documents, IRB approval notices, and signed, dated, and completed case report forms (CRFs), medical records including, for example, progress notes of the physician, the subject’s hospital chart(s) and the nurses’ notes.

Such records shall include:

• Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, and written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent.

• All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each participant upon entering and during the course of the investigation, including information about relevant previous medical history and the results of all diagnostic tests.

• A record of the exposure of each participant to the investigational device, including the date and time of each use, and any other therapy.

• The protocol, with documents showing the dates of and the reasons for each deviation from the protocol.

• Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

For a complete list of essential documents, see ICH E6 S8

An investigator or sponsor may withdraw from the responsibility to maintain records for the period required in 21 CFR 812.140(d) and transfer custody of the records to any other person who will accept responsibility for them under 21 CFR 812.140, including the requirements of 21 CFR 812.145 [21 CFR 812.140(e)]. Notice of this transfer shall be given to the FDA not later than 10 working days after transfer occurs.
What are the sponsor-investigator's responsibilities as a sponsor?

The sponsor-investigator carries all responsibilities toward co-investigators that are normally assigned to the sponsor.

1. General responsibilities of sponsors 21 CFR 812.40
   The sponsor-investigator is responsible for
   a. selecting qualified investigators and providing them with the information they need to conduct an investigation properly.
   b. ensuring proper monitoring of the investigation. For more information on monitoring guidelines, see Section 5.18 of the ICH Guidance.
   c. ensuring that IRB review and approval are obtained.
   d. submitting an IDE application to the FDA.
   e. ensuring that any reviewing IRB, FDA, and participating investigators are promptly informed of significant new information about an investigation.

2. Selecting and monitoring investigators 21 CFR 812.43 – 812.46
   The sponsor-investigator is responsible for
   a. selecting qualified investigators and monitors.
   b. ensuring that the investigational device is shipped only to participating investigators.
   c. obtaining investigator agreements.
   d. obtaining statements from participating investigators attesting to their commitment to the proper conduct of the investigation.
   e. obtaining accurate financial disclosure statements from participating investigators.
   f. providing participating investigators with the investigational plan.
   g. informing co-investigators of new observations with regard to the investigational device and progress of the study.
   h. reviewing on-going investigations, including assuring compliance of all investigators with the protocol, reviewing and evaluating safety and efficacy data of the investigational device, and discontinuing studies that are deemed to pose an unreasonable and significant risk to subjects.

3. Adverse device effects and study termination 21 CFR 812.46
   - The sponsor-investigator must immediately evaluate any unanticipated adverse device effect. If the sponsor-investigator determines that the device presents an unreasonable risk to subjects, the sponsor-investigator must terminate the study within 5 working days after making this determination, but not later than 15 working days after first receiving notice of the adverse effect.
   - If the device is significant risk, the sponsor-investigator may not resume a terminated investigation without IRB and FDA approval.
   - If the device is nonsignificant risk, the sponsor-investigator may not resume a terminated investigation without IRB approval.

4. Recordkeeping and record retention 21 CFR 812.140
   The sponsor-investigator is responsible for maintaining study records, as described above.

5. Inspection of sponsor’s records and reports 21 CFR 812.145
   The sponsor-investigator must allow FDA employees access to all records and reports at their request. An investigator who has authority to grant access shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any
establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept). [21 CFR 812.145(a)].

An investigator shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation. [21 CFR 812.145(b)].

An investigator shall permit authorized FDA employees to inspect and copy records that identify participants, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading. [21 CFR 812.145(c)].

**What are the sponsor-investigator’s responsibilities as an investigator?**
As an investigator, the sponsor-investigator has all the responsibilities of investigators in any clinical trial.

1. **General responsibilities of investigators 21 CFR 812.100**
   An investigator may determine whether potential participants would be interested in participating in an investigation, but shall not request the written informed consent of any participant to participate, and shall not allow any participant to participate before obtaining IRB and FDA approval. [21 CFR 812.110].
   The investigator is responsible for providing a letter or an e-mail from the FDA (as an attachment to the HawkIRB system) giving the IDE number, if applicable, as assigned by the FDA.
   The sponsor-investigator is responsible for
   - ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable FDA regulations.
   - protecting the rights, safety, and welfare of subjects under the investigator’s care
   - ensuring the control of devices under investigation.

2. **Compliance with protocol 21 CFR 812.110b**
   The sponsor-investigator must conduct the investigation in accordance with the signed agreement, the investigational plan, FDA regulations, and IRB conditions. [21 CFR 812.110]

3. **Device use and disposition 21 CFR 812.110c**
   The sponsor-investigator must permit the use of an investigational device only with subjects under the investigator’s supervision. Upon completion or termination of a clinical investigation or the investigator’s part of an investigation, or at the sponsor’s request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs. [21 CFR 812.110]

4. **Investigator recordkeeping and record retention 21 CFR 812.140a**
   The sponsor-investigator is responsible for maintaining study records, as described above.

5. **Investigator reports 21 CFR 812.150**
   The sponsor-investigator must provide reports to the FDA as described above.

6. **Inspection of investigator’s records and reports 21 CFR 812.145**
   The sponsor-investigator must allow FDA employees access to all records and reports at their request.
Placebo-Controlled Trials

If an investigator proposes a study in which a placebo is given for any length of time in lieu of
an approved FDA indicated drug, the investigator must include risk management procedures in the
research plan for the IRB for review. To the extent that the investigator demonstrates that the
subjects’ safety is monitored at all times and provisions are made for immediate rescue if needed,
the IRB will consider approval of the study.

Once an approval is granted, the investigator is bound to follow the risk management
procedures as with any other provision of the approved protocol. Use of placebos may be
appropriate where the investigator demonstrates that:

• standard therapy is unavailable or is of unproved efficacy, or
• standard therapy possesses unacceptable side effects, or
• minimal harm may result from the use of placebo (e.g., ongoing disease has little adverse
effect on the patient during the course of the trial and is reversible), or
• placebo itself may be an effective therapy, or
• the disease process is characterized by exacerbation and remission.

The risk management procedures should be in the written protocol, with the same level of
detail as in the protocol itself. The following issues should be specified:

• the frequency of monitoring,
• whether monitoring is in person or by telephone,
• the criteria for managing a subject in the event of worsening, and
• how 24 hour-per-day, 7 day-per-week, medical care is made available in the event of
questions, emergencies, worsening, or withdrawal from the protocol.

The IRB may make its decision based upon the extent to which the above factors are
demonstrated and upon a relative weighing of these and other factors. In discussing potential
harm from the use of placebos, the investigators must provide a procedure for adequate
monitoring of subjects to ensure their safety.

Specimens – see Data/Specimen Collection Above
State of Iowa Laws

Iowa state law on the legal age to consent to treatments or procedures (see Chapter 5, Section A for Individuals in the State of Iowa that meet the FDA and DHHS definitions of child and guardian)

Iowa state law provisions on mandatory reporting:
1. Current abuse of a dependent adult (see Iowa Code Chapter 235 B):

"Dependent adult" is defined in §235B.2(4) as follows:
"Dependent adult" means a person eighteen years of age or older who is unable to protect the person's own interests or unable to adequately perform or obtain services necessary to meet essential human needs, as a result of a physical or mental condition which requires assistance from another, or as defined by departmental rule.

2. Current child abuse (see §232.69)
Note: §232.69(2) refers to permissive reporters ("any other person (i.e., other than listed in (1)) who believes that a child has been abused may make a report").

3. Other reporting
The general licensing provisions for a number of health care professions (see Iowa Code Chapter 147) require reporting a wound or "other serious bodily injury" that is being treated by the person licensed under that chapter and that appears to have been received in connection with the commission of a criminal offense.

Reportable conditions (see §641--1.1-1.3 (139A))
Additional state laws provide for the notification and surveillance of reportable communicable and infectious diseases, poisoning and conditions. Of note, in Iowa these include cancer and birth defects with reporting to the State Health Registry located at UI. When it is possible that identification of a reportable condition may occur in the research setting, investigators must include this information and the reporting requirements in the informed consent document.

Intent to hurt self or others
Common law (not statute) generally requires that one report a demonstration of a current intent to hurt oneself or others.

Iowa state law prohibition on human cloning (§707B.4).
A person shall not intentionally or knowingly do any of the following:
- Perform or attempt to perform human cloning.
- Participate in performing or in an attempt to perform human cloning.
- Transfer or receive a cloned human embryo for any purpose.
- Transfer or receive, in whole or in part, any oocyte, human embryo, fetus, or human somatic cell, for the purpose of human cloning.

This section shall not restrict areas of scientific research not specifically prohibited, including in vitro fertilization; the administration of fertility-enhancing drugs; or research in the use of nuclear transfer or other cloning techniques to produce molecules, deoxyribonucleic acid, tissues, organs, plants, animals other than humans, or cells other than human embryos. This
law does not prohibit using stem cells from cloned embryos that are cloned in another state as long as all that is received at the UI is the stem cells.

Applicability of the laws of other states

In cases of human subjects research under the authority of the UI IRB(s) but conducted outside of the state of Iowa, the UI IRB confers with the UI Office of General Counsel regarding the applicability of other state, national, or international laws to the particular project. These cases are identified in the pre-review process of an application to the IRB and the advice of counsel is sought prior to the approval of the study. In general, the UI IRB will apply the law of the state in which the research is being conducted. For example, if a project involves children and one of the recruitment sites is in a bordering state, the laws of the bordering state will be evaluated to which individuals meet the DHHS and FDA definition of “children” at that site.
Surveys, Questionnaires, and Interview Studies

Not all survey, questionnaire, or interview research is minimal risk. For example, a survey or interview that asks questions about sensitive topics (e.g., childhood abuse, sexual functioning) likely to cause emotional stress or discomfort may require full IRB review. Some survey research may be classified as exempt from the regulations if the information obtained is recorded in a way that the subject cannot be identified (either directly or through a code numbers or link); in other words, if the research data are anonymous.

The term anonymous is sometimes confused with the term confidential. In human subjects research, anonymous means that at no time during the data collection could someone determine who provided the information. If a link existed at any time, even if the link is subsequently destroyed, the IRB cannot consider the information anonymous.

A survey or interview study may also be considered exempt from the regulations even when the data are not anonymous if the information being gathered could not reasonably place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation. The most common classification for survey, questionnaire, or interview research is expedited approval. If the study is not anonymous and contains information that, if known, could be damaging as described above, but it does not rise to the level of more than minimal risk, it may be given expedited approval. Although the New Project application gives the investigator the opportunity to indicate a classification, the chairs or his/her IRB member designee make the final determination as to the classification of exempt or expedited.

For minimal risk mail-out or web-based surveys or questionnaires, it may be appropriate to request that the chair or his/her IRB member designee waive the requirement for the subject's signature on an Informed Consent Document. When the subject's signature requirement is waived, generally the investigator provides all of the required elements of consent in a cover letter, with a statement that returning the survey or questionnaire will be considered voluntary agreement to participate. For additional information on waiver of signature, see Chapter 5.
Washout Issues in Drug Treatment Studies

When a subject is asked to stop taking some or all medications prior to beginning a drug treatment study, this is called a drug washout. Washouts are appropriate depending upon the disease to be studied and the nature of the proposed protocol. Washout studies require balancing the likelihood of harm, the effectiveness of monitoring, and the potential severity of the risk(s) to be avoided. When subjects are being washed out from a FDA approved and indicated drug, the individual investigator should clearly define the nature and degree of risk to the subjects and include risk management procedures in the research plan. To the extent that the investigator demonstrates that the subjects' safety is monitored at all times and provisions are made for immediate rescue if needed, the IRB will consider approval of the study. Once an approval is granted, the investigator is bound to follow the risk management procedures as with any other provision of the approved protocol. The risk management procedures should be in the written protocol, with the same level of detail as in the protocol itself. The following issues should be specified:

* careful definition as to when a subject would be withdrawn from the study,
* the frequency of monitoring,
* whether monitoring is in person or by telephone,
* the criteria for managing a subject in the event of worsening, and
* how 24 hour-per-day, 7 day-per-week, medical care is made available in the event of questions, emergencies, worsening, or withdrawal from the protocol.
Chapter 10 – Allegations of Noncompliance

The Principal Investigator bears the ultimate responsibility for the conduct of a research project. The investigator must comply with the requirements of the University of Iowa’s Federalwide Assurance and with determinations of the IRB, as outlined in minutes and other correspondence. Information regarding noncompliance in human subjects studies may come to the attention of the IRB through several pathways. These include information contained in application forms, IRB reporting forms, monitoring reports, or reports from collaborators, employees, subjects, or others not directly involved in the research.

When information comes to the attention of the IRB outside of a full-board meeting, the Chair of the appropriate IRB reviews the allegations of noncompliance. The Chair makes a determination as to whether the alleged practices appear to (1) cause injury or any other unanticipated problems involving risks to subjects or others, or (2) constitute serious or continuing noncompliance with IRB determinations or federal regulations. In such cases, the Chair may suspend the study procedures, taking into consideration the welfare of currently enrolled subjects, pending an investigation and review by the full IRB. If the Chair determines that the potential noncompliance did not involve any risk to subjects or others, and did not constitute serious or continuing noncompliance, the Chair may resolve the issue directly with the Principal Investigator and research team.

When potential noncompliance is first identified during a full-board review, the full-board makes a determination as to whether the alleged practices appear to (1) cause injury or any other unanticipated problems involving risks to subjects or others, or (2) constitute serious or continuing noncompliance with IRB determinations or federal regulations. In such cases, the full board may suspend the study procedures, taking into consideration the welfare of currently enrolled subjects, and determine how further investigation will be conducted according to the procedures indicated below.

In cases that involve allegations of research misconduct, the Chair contacts the UI Research Integrity Officer (RIO) for further action. This does not preclude the Chair or any member of the IRB from independently contacting the RIO about any allegation of scientific misconduct. Inquiries or investigations into research misconduct do not preclude IRB review and actions.

The following points outline procedures for investigating and resolving alleged noncompliance:

1. When made aware of an allegation of noncompliance, HSO staff immediately notifies the UI IRB Chair for the IRB of record and works with the Chair to compile any required background file information. If the alleged noncompliance involves a WIRB or CIRB study, the allegation is reported to an IRB-01 Chair who in turn immediately notifies the appropriate IRB of record.

2. The UI IRB Chair makes a determination as to whether to pursue the matter with the Principal Investigator via telephone call, e-mail, paper memo, or in person based on the nature and seriousness of the alleged noncompliance. The Chair may also choose to send an IRB monitor to meet with research team members and review study materials as appropriate. The purpose of such contact is fact-finding, i.e. to determine if indeed there is noncompliance. Care is taken to maintain confidentiality when leaving messages for the Principal Investigator via voice mail or with secretarial and support staff. For WIRB or CIRB studies, the UI IRB Chair coordinates the UI investigation with the IRB of record. Investigations are initiated within 5 working days of initial notification.

3. The UI Chair and/or monitor document the outcome of any and all communications and discussions in writing, by either e-mail or paper memo with a copy to the IRB files. Such documentation should be factual and objective, and include timelines for resolution (e.g. meeting dates, response deadlines).
4. The UI Chair makes a decision based on the information gathered as to whether the allegation is credible.

5. If the UI Chair believes the allegation is credible, the UI Chair determines whether the noncompliance meets the definition of serious or continuing noncompliance, or is included in a category for full board review according to the UI IRB Monitoring Guidelines. In making this determination, the Chair may bring the issue to the appropriate Chairs’ meeting for discussion.

   a. If the Chair determines that the noncompliance is not serious or continuing, does not involve unanticipated risk to subjects or others, and is not in one of the categories requiring full board review according to the UI IRB Monitoring Guidelines, the Chair and PI work together to create an acceptable corrective action plan.

   b. If the Chair determines that the noncompliance is serious, continuing, involves unanticipated risk to subjects or others, or is in one of the categories requiring full board review according to the UI IRB Monitoring Guidelines, the Chair refers review of the noncompliance to the next available IRB-01 Executive Committee meeting (or regular full board meeting if the Chair determines that resolution is required in a more timely fashion due to potential risk to subjects or others) or IRB-02 regular meeting. If the Chair believes that the noncompliance is serious or continuing and that there is continuing risk of harm to current or future subjects, the Chair may suspend research activities, taking into consideration the welfare of currently enrolled subjects, until review by the full board.

   • A primary reviewer is assigned to lead the discussion at the full board meeting. All IRB members including the primary reviewer receive appropriate materials such as monitoring report(s), communications with the Principal Investigator or other relevant individuals, and Reportable Events Forms (if applicable) for their review. Approved IRB applications, consent documents and other documentation from the project file may also be included as reference materials during the review and are distributed to all IRB members prior to the full board meeting. All IRB members are expected to review and be familiar with all materials.

   • When a quorum of IRB members is present, and after discussion, the IRB shall vote recommended actions.

   • The possible actions that could be taken by the IRB include:
     o Suspension or termination of IRB approval of protocols that are found to be noncompliant with institutional policies and procedures, state laws, and/or federal laws or regulations, taking into consideration the welfare of currently enrolled subjects,
     o Compliance audits,
     o Letters of reprimand,
     o Restrictions on serving as an investigator on human subjects protocols,
     o Notification of currently enrolled subjects,
     o Providing additional information to past subjects,
     o Modification to research protocols,
     o More frequent continuing review or monitoring,
     o Monitoring of the consent process,
     o Changes in consent process or documents,
     o Requirement that currently enrolled subjects re-consent to participation,
     o Request more information prior to making a final decision,
Referral of the issue to other organizational entities such as UI legal counsel, risk management, or the research integrity officer, or
Other actions as appropriate.

The IRB determines which sanctions and/or requirements must be met for the study to proceed. If the investigator can meet these sanctions/requirements with simple concurrence, the IRB Chair determines when these are met and gives approval for the study to recommence. If sanctions or requirements require more than simple concurrence, the issue is returned to the full board for consideration of resumption of the research project.

- The IRB determines whether the noncompliance meets the definition of serious or continuing noncompliance.

**What is serious noncompliance?**
Serious noncompliance is noncompliance that results in unexpected harm to subjects or others. This type of noncompliance may harm a person’s physical, social, emotional, psychological well-being, social or legal welfare, or cause harm due to loss of the person’s privacy or confidentiality.

**What is continuing noncompliance?**
Any noncompliance that occurs repeatedly to the point of suggesting a pattern or an underlying problem. Continuing noncompliance may occur due to a lack of knowledge (unintentional) or due to deliberate choice to ignore regulations or determinations of the IRB (intentional).

- The IRB sends written notification of actions taken to the principal investigator.
Chapter 11 – Investigator Questions, Concerns and Suggestions

Staff in the HSO are available to investigators and their research team members to answer questions about the IRB review process. A staff listing along with their areas of expertise may be found on the HSO website. If the HSO is unable to help with your issue, you may also contact the Office of the Vice President for Research at 335.2119.