Protecting Human Subjects Guide

This Guide has been provided by the Research Subjects' Protection Programs Staff to assist researchers in preparing their application for review of research involving human subjects in accordance with the guidelines set forth by the University.
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1. **THE IRB AT THE UNIVERSITY OF MINNESOTA**

Protecting human subjects involved in research is a collaborative effort that demands the vigilance of University faculty, staff, and students in partnership with the local community and federal agencies. This guide through the peer review process is intended to help researchers meet their responsibilities.

1.1 The IRB's charge
1.2 The membership and structure of the IRB
1.3 Research subjects' protection programs
1.1 The Institutional Review Board's charge

The charge of the University of Minnesota's Institutional Review Board (IRB) is:

- to protect human subjects involved in research at the University from inappropriate risk and
- to ensure that human subjects consent to their research participation.

The Institutional Review Board (IRB) was formally established at the University of Minnesota in the early 1970s as the "Committee on the Use of Human Subjects in Research". The Regents' most recent policy statement, Research Involving Human Subjects, was adopted by the Board of Regents on July 8, 1994.

The basis for the Regents' policy and the IRB charge is found in the Code of Federal Regulations (CFR). Although protection of research subjects is a concern of all federal agencies that sponsor research, leadership is vested in the Office for Human Research Protection (OHRP) and the Food and Drug Administration (FDA). The OHRP has general responsibility for the protection of humans as subjects in research, and the FDA regulates the use of drugs and medical devices in experiments.

The OHRP's primary method of regulating compliance of institutions is through "assurances." FederalWide Assurance (FWA) is an agreement with OHRP approved for three-year intervals. The University's assurance identifies our responsibilities and explains the steps that we will take to meet the federal regulations for research on human subjects. Under certain conditions, additional assurance documents must be filed.

1.2 Membership and structure of the IRB

The IRB is composed of more than 60 members representing University faculty, staff, students, and the local community. The committee strives for a balance of men and women and representation from minority populations. Representatives from the University of Minnesota campuses at Duluth and Morris also serve on the IRB.

The members bring diversity in experience and expertise, which enables the IRB to evaluate a wide range of research. The professional preparation of IRB members includes:

- expertise in a range of research areas,
- familiarity with applicable laws and regulations with relevant standards of professional conduct and practice, and
- knowledge of vulnerable or special populations such as children, prisoners, pregnant women, and disabled persons.

The IRB is divided into six panels. Four panels review research in the health and biological sciences, one reviews research in the social and behavioral sciences, and the sixth is an executive committee that addresses policy issues and provides guidance to the other five panels. Members are assigned to panels on the basis of the panels' needs and the members' interests and expertise.

1.3 Authorities of the IRB

To carry out its charge of protecting human subjects as required under federal regulations and Regents Policy, the IRB has the following responsibilities and authorities:

1. The IRB reviews and has authority to approve, require modifications of, or disapprove all University research involving human subjects. No other University official may approve human subjects research if it has not been approved by the IRB.
2. The IRB monitors and conducts continuing review of approved research at intervals of at least once per year. As part of this responsibility, the IRB has authority to observe or have a third party observe the consent process and the research.
3. The IRB has authority to inspect research facilities and obtain records and other relevant information relating to the use of human subjects in research.

4. The IRB takes such actions that are necessary in its judgment to comply with federal regulations or other applicable laws, including action to suspend or terminate approval of research that is not being conducted in accordance with the IRB’s requirements or that has been associated with unexpected serious harm to subjects.

5. The IRB reports to appropriate University and federal government officials:
   a. any unanticipated problems involving risks to subjects or serious or continuing noncompliance with IRB requirements; and
   b. any suspension or termination of IRB approval of research.
2. What Is Subject to Review?

The scope of the Institutional Review Board's (IRB) charge is broad. Generally, any University research that uses humans, human tissue, surveys of human subjects, or human subjects' records requires IRB review, irrespective of its funding source. The IRB's charge extends to research in the social and behavioral sciences as well as research in the health and biological sciences.

2.1 Scope of review

2.2 Research at Fairview Health System and Gillette Children’s Specialty Hospital

2.3 Research at "affiliated faculty"

2.4 Research projects in which the researcher is a consultant

2.5 Research by students--the faculty responsibility

2.6 Research in university courses

2.7 Research at another institution

2.8 Research that is part of multicenter clinical trials

2.9 Research in foreign countries

2.10 Research at a pilot or feasibility stage

2.11 Research involving secondary use of data

2.12 Research using "waste" and "extra" material
2.1 Scope of review

IRB review and approval is required for any research involving human subjects that:

- is conducted by University faculty, staff, students, Fairview or Gillette employees;
- is performed on the premises of the University, Fairview Health Services or Gillette Children’s Specialty Hospital;
- is performed with or involves the use of facilities or equipment belonging to the University;
- involves University patients, students, staff, or faculty;
- involves Fairview Health Services or Gillette Children’s Specialty Hospital patients and/or patient data;
- satisfies a requirement imposed by the University for a degree program or for completion of a course of study; or
- is certified by a dean or department head to satisfy an obligation of a faculty appointment at the University, including clinical or adjunct appointments.

2.2 Research conducted by Fairview Health System

Research involving human subjects conducted at Fairview must meet the requirements set down by the Fairview "Research Involving Human Subjects Policy" (http://www.fairview.org/prof/research/human_subj.asp)

Other Fairview research policies related to subject protection can be found at http://www.fairview.org/prof/research/research_pol.asp.

2.3 Research conducted by "affiliated faculty"

Research conducted by "affiliated faculty"—faculty members who hold clinical or adjunct appointments—is subject to the University's guidelines for research on human subjects and must be submitted for IRB review. Any research project that is conducted by or under the direction of any employee or agent of this institution, in connection with his or her institutional responsibilities, requires IRB approval.

2.4 Research projects in which the researcher is a consultant

University IRB review is required unless the researcher has a strict consulting relationship in which:

- the researcher is hired on his or her own time,
- the researcher holds no rights in the work, and
- neither the researcher nor the University retains any data.

All three of these criteria must be met, or the IRB will need to review the project.

2.5 Research conducted by students--the faculty responsibility

Independent class projects, senior theses, undergraduate research projects, master's projects, and similar exercises must be independently submitted to the IRB by the student-researcher. However, when students conduct research as part of a course of study, a faculty member ultimately is responsible for the protection of the subjects, even if the student is the primary researcher and actually directs the project. Advisers shoulder the responsibility for students engaged in independent research, and instructors are responsible for research that is conducted as part of a course.

During the design of a project, advisors and faculty members should instruct students on the ethical conduct of research and help them prepare applications for IRB approval. In particular, students should:

- understand the elements of informed consent,
- develop a readable consent form following the sample (http://www.irb.umn.edu/consent/),
• plan appropriate recruitment strategies for identifying subjects,
• establish and maintain strict guidelines for protecting anonymity and confidentiality, and
• allow sufficient time for IRB review and completion of the project.

As assurance that the University's guidelines will be followed, the adviser or instructor is required to sign the student's application for IRB approval.

After IRB approval, faculty members should take an active role in ensuring that projects are conducted in accordance with the IRB's requirements. Meeting periodically with students to review their progress is one way to meet this responsibility.

2.6 Research conducted in university courses

Courses in research methods and class assignments that involve research with human subjects require IRB approval even if the class exercise does not seem to qualify as "true research": when, for example, the results are not intended for publication, will not advance work in another area, or will not contribute to generalizable knowledge. The IRB reviews research for risk assessment and provisions for informed consent.

See section 3.6 Class Protocols for Research Methods Courses

2.7 Research conducted at another institution

For a University researcher to participate in a research project at another site, the project needs to be reviewed by the University of Minnesota IRB as well as by the other institution's IRB. For example, a University researcher engaged in research at the Veterans Administration Medical Center must secure approval from both institutions' IRBs.

The IRBs in the Twin Cities try to accommodate researchers who work at multiple sites by streamlining the IRB approval process. In some cases, reciprocal review and approval arrangements with the University IRB relieve the investigator of obtaining the independent approval of two IRBs. For more information, contact the IRB.

Researchers who must submit a project to another IRB should include copies of the application and review of the University of Minnesota IRB. Changes in protocol or consent forms required by the other IRB should be brought to the attention of the University IRB.

2.8 Research that is part of multicenter clinical trials

Approval of a proposal document at the national level is not sufficient to bypass approval at the local level. Researchers who conduct multicenter clinical trials sponsored by the National Institutes of Health (NIH) or the National Cancer Institute (NCI), for example, should include protocols and consent forms approved at the national level with their applications to the University IRB. Although the documents should be identified as having been approved by a national IRB, the local IRB must review the material as it would any other submission.(OHRP Report Number 93-01).

Only the local IRB is vested with the authority to review and approve projects to be conducted at a given institution familiar with the particular circumstances of its research setting and is able to weigh critical considerations such as state and local laws, professional and community standards, institutional policies, and the needs of different patient and subject populations.

If changes are made to documents approved by the national IRB, the investigator must notify that IRB. The University IRB will rarely make substantive changes in the protocol or study plan and more likely to request that the wording of a consent form be changed to reflect local standards or to include specific language required by the University.

2.9 Research in foreign countries
Research conducted by University investigators in foreign countries remains under University purview and guidelines. While we cannot impose our standards for written documentation on other cultures, we do not relax our standards for ethical conduct or consent process.

While human subjects in foreign countries merit the same level of protection as subjects in the United States, acceptable practices vary from place to place. Different mores, traditions, and institutions may require different research protocols, particularly in informed consent, recruitment practices, and documentation. Special attention should be given to local customs and to local cultural and religious norms in drafting written consent documents. Research projects must have been approved by the local equivalent of an IRB before they are presented to the University IRB. Where there is no equivalent board or group, investigators must rely on local experts or community leaders to provide approval. The IRB requires documentation of this "local approval" before it gives approval. Researchers should describe what if any, knowledge or experience they possess regarding the language and culture of the country in question.

The Office for Human Research Protection (OHRP) can determine whether procedures described by a foreign institution afford protections that are at least equivalent to U.S. regulations (45 CFR 46 101 [h]). Under this provision, OHRP investigates the foreign country's guidelines for human subjects research, and if the foreign guidelines are found to be equivalent to U.S. regulations, the investigator is permitted to substitute those foreign procedures. Researchers proposing international research should allow additional time for this review process.

2.10 Research at a pilot or feasibility stage

Pilot studies and feasibility studies, including those involving only one human subject, require the same scrutiny as full-scale research projects. Pilot studies should be identified as such in applications to the IRB. Ordinarily the data collected from subjects in a pilot/feasibility study are not used for study findings.

It must be explained to subjects during the consent process that the study is a pilot.

2.11 Research involving secondary use of data

Projects that use data on human subjects gathered in earlier projects require IRB review. If the data are gathered by someone who has legitimate access to the records and who gives the investigator only "blinded" or de-identified data (so that the investigator is unable to identify the subjects), the level of risk is lowered.

2.12 Research using "waste" and "extra" material

Research that is conducted on "waste" or "extra" human tissue or fluids must be submitted for review. "Waste material" is material that is collected originally for clinical or diagnostic purposes only but is no longer needed. "Extra material" is material that is collected above and beyond what is needed for a clinical or diagnostic procedure. It is collected during the same procedure, but solely for investigational purposes.

The IRB may determine that research on waste material qualifies as exempt from full review. If the subject's consent to the clinical procedure outlines research use of the material as well, a separate consent form may not be required. Collecting and using "extra material" requires subjects' written consent and full IRB review.
3. **How to Apply for Review**

The central task of the Institutional Review Board (IRB) is to ensure that a project's risks are justified by its benefits.

3.1 The IRB process
3.2 Primary types of review
3.3 Screening for exempt status
3.4 Expedited review
3.5 Full review
3.6 Course protocol review
3.7 Application forms and original signatures
3.8 Preparing the application
3.9 Designating the principal investigator
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3.20 Labeling investigational drugs
3.21 Research involving ionizing radiation
3.22 Emergency waivers
3.1 The IRB process

The IRB reviews a proposal by first assessing the risks and benefits of research participation. After determining that the research benefit outweighs the risks involved, the IRB turns to the consent process to ensure that subjects are fully aware of the risks and the benefits and that they participate in the project voluntarily. The consent form is a key element in this review.

After reviewing the application and its supporting materials, the IRB may require revisions in the protocol. When the investigator revises a project, the IRB reviews the project again to see whether its concerns have been adequately addressed. A project may undergo several reviews.

To fully protect subjects, the IRB must approve a project before investigators start to work on it—even before they begin to recruit subjects, since recruitment strategies are part of the review. Although there are different types of review, many projects require "full" committee review. The initial full review will occur within two weeks of submission if the application is complete. All IRB actions are communicated in writing to the investigator by the IRB staff.

3.2 Primary types of review

Research projects are reviewed at one of three levels, according to the IRB's determination of the project's potential risk to the human subjects and the federal guidelines that define the categories of review, which are:

- screening for exemption from full IRB review,
- expedited IRB review, and
- full convened IRB review.

The level of review is determined only by the IRB.

3.3 Screening for exempt status

Investigators do not have the authority to determine whether research involving human subjects is exempt from full review (45 CFR 46.101(b) and (c). Hence, while research that involves only minimal risk to human subjects is sometimes exempt from full IRB committee review, it is still subject to IRB review. Researchers must file an application requesting that the IRB determine exempt status for a project.

In general, the federal guidelines for research on human subjects allow a project to be exempt from full review only if the research involves no risk to the subject and the procedures are limited to the following criteria:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instruction, 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 that is not exempt under paragraph (b)(2) of this section, 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.

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 payment for benefits or services under those programs.

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 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.

Projects that involve contact with subjects may still qualify as exempt. Copies of the written consent form should be
filed with the application or justification for a waiver of written documentation should be provided. See 45 CFR
46.117.

The application form, titled Screening for Exemption Application Form, is available from the Research Subjects'
Protection Programs office or its Web site (http://www.irb.umn.edu).

The IRB administrator decides whether the project qualifies as exempt, and the decision is confirmed in writing, most
often within one week. If the project does not qualify as exempt, it is referred back to the investigator with the
appropriate application forms.

3.4 Expedited review

To qualify for expedited review, a research procedure must be limited to the activities that are federally approved (from
63 FR 60364-60367, November 9, 1998.) for expedited review and incur no more than minimal risk for participants,
or be a minor change in previously approved research that involves no additional risk to the research subject.
The activities approved in the federal regulations for expedited review are:

1. Clinical studies of drugs and medical devices
2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture
3. Prospective collection of biological specimens for research purposes by noninvasive means
4. Collection of data through noninvasive procedures
5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be
   collected solely for nonresearch purposes
6. Collection of data from voice, video, digital, or image recordings made for research purposes
7. Research on individual or group characteristics or behavior
8. Continuing review of research previously approved by the convened IRB
9. Continuing review of research, not conducted under an investigational new drug application or investigational
device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and
documented at a convened meeting that the research involves no greater than minimal risk and no additional
risks have been identified

The researcher must demonstrate in the application how the proposed project activities fall into one or more of these
categories.

To apply for expedited review, investigators complete either the Health & Medical/Biological or the Social &
Behavioral Sciences Application Form and indicate that they are requesting expedited review in the appropriate
section.
The IRB administrative staff assures that all of the elements essential for review, including consent forms and supporting information, have been submitted. The application is then forwarded to a designated committee member for review and decision. Either the research is approved (perhaps with stipulations) by the committee member or it is forwarded for full review.

### 3.5 Full review

A project that involves greater than minimal risk requires approval by an IRB panel composed of members qualified to review research in that field. Research that requires full committee review includes:

- research that involves greater than minimal risk
- non-exempt research that involves children or other vulnerable populations;
- research that involves experimental drugs or devices;
- research that involves invasive procedures; and
- research that involves deception.

Survey research that involves sensitive questions or information about sexual practice or illegal behavior is subject to full review, in keeping with federal guidelines. Any survey or interview that is likely to be stressful for the subject requires full committee review. IRB staff will make this determination.

All applications are screened by the administrative staff before they are assigned to an IRB panel; if the application is incomplete, it is returned to the investigator. After review by the IRB panel, the application will be:

- approved as submitted;
- approved with minor suggestions for changes;
- approved with stipulations (conditions that must be met before final approval is granted) - most common;
- deferred, pending receipt of additional information or major revisions; or
- not approved.

All non-exempt research is subject to continuing review at least annually[see 6.1 Continuing Review]. If research involves significant risk to subjects, the IRB may require more frequent review and may ask to be kept apprised of all research activity. For example, researchers in acute care settings or whose research involves novel therapies are asked to submit their protocols for frequent review.

### 3.6 Class Protocols for Research Methods Courses

If the overall objective of a course assignment is to learn about the design and conduct of research projects, and if data will be collected and analyzed for classroom learning only, a request for approval of a class protocol should be filed with the IRB office.

If the same class protocol will be used in several courses during an academic year, the IRB may be able to approve all uses with a single application. The protocol must be reevaluated annually, however, to ensure that the guidelines are maintained and to bring the protocol up to date with any changes in the federal guidelines.

Very ambitious projects and projects that involve sensitive topics and vulnerable populations are not suited to the class protocol review process. These must be pursued as individual projects.

An example of an acceptable class protocol is a course in psychology taught several times per year by different faculty members. The course involves a cluster of independent projects conducted by the students. In this case, students complete IRB application forms and submit them to their instructors for review and approval. The course protocol adheres to the following terms:

- the instructor will direct students to complete basic level training for human subject protection
- student projects will be reviewed by course faculty;
• students will draw their research subjects from the student population (if extra credit points are awarded to subjects, a faculty member will determine whether the points awarded are appropriate in light of the time spent by the subject);
• student projects will not involve any personal, sensitive, or incriminating topics or questions that could place subjects at risk;
• the projects will not manipulate the behavior of students in any way beyond the range of normal classroom activity or college life; and
• the projects will not involve physically invasive contact with the subjects.

Please see sections 2.5 and 2.6 to find more about research in classes and by students

3.7 Application forms and original signatures

All forms that an investigator must file with the IRB to apply for review are available, with specific instructions, on the Web at http://www.research.umn.edu/subjects, or from the Research Subjects’ Protection Programs (RSPP) office. The RSPP staff can help researchers determine which level of review is appropriate for a project. The forms are:

- Screening for Exemption Application Form
- Health & Medical/Biological Application Form (expedited or full review)
- Social & Behavioral Sciences Application Form (expedited or full review)

Providing original signatures

A signature page provides space for the signature of the principal investigator and co-investigators. Original signatures are required here. An original signature certifies that the investigator will be actively involved in the research project and has made a commitment to protect the research subjects according to the federal regulations.

Others besides the investigators need to sign, too. Academic advisers must sign all student research proposals, and department heads must sign all faculty, staff and student proposals. Some colleges and campuses have imposed additional signature processes. Check with your local department to assure compliance.

All other documents submitted to the IRB (such as interim reports, requests for changes in protocol, reports of adverse events, requests for renewal of approval) must be accompanied by correspondence signed by the principal investigator. Staff signatures are not accepted. The principal investigator remains ultimately responsible for protection of subjects.

Finally, before submitting the application with original signatures, investigators must:

- make a copy of the application for their own records, and
- make multiple copies for the IRB:

For full IRB review, attach:

- 12 copies of the application,
- 12 copies of the consent form,
- 1 copy of the complete protocol, and
- Any additional information.

For expedited review, attach:

- 3 copies of the application,
- 3 copies of the consent form,
- 1 copy of the complete protocol, and
- Any additional information.
3.8 Preparing the application

To submit a project to the IRB for review, an investigator must complete the application form according to detailed instructions and enclose supporting material as necessary.

A fully completed application form will include:

a. an up-to-date version of the appropriate application form,
b. answers to every question on the form,
c. appropriate appendices to the application,
d. a lay abstract describing the purpose of the study,
e. a description of the study population, criteria for including and excluding participants, the number of and the process of identifying subjects, and any other plans related to the selection of subjects,
f. a description of the tasks that subjects will be asked to perform,
g. a full description of the anticipated risks and benefits of participating in the study,
h. an outline of strategies for minimizing risks,
i. documentation of provisions to care for subjects in case of accident or injury,
j. a full description of procedures for maintaining confidentiality,
k. a description of the process by which informed consent will be obtained from the appropriate individuals (for example, subjects, parents, cooperating institutions),
l. documentation of any required approvals or applications for approval from other committees and from cooperating agencies,
m. all supporting materials and documents, including protocol, interview schedules, solicitation letters, advertisements, descriptions of any medications, and any survey instruments that are rarely used or are designed by the investigator (common standardized instruments can be merely cited), and
n. appropriate original signatures, including an academic adviser's signature for student research and department head signatures for all research.

The application form alone will be used as background information for all future reviews of the study; therefore, "see protocol" is not an adequate response to any application question.

No form can adequately address the wide diversity of research at such a large institution. Principal investigators should use the form to convey the nature and specifics of the project proposed attaching appendices as necessary.

3.9 Designating the principal investigator

A research project is headed by a principal investigator (PI). At one time, federal regulations for human subjects research allowed the PI to shoulder most of the responsibility for a project. Recently, though, the regulations have emphasized that the whole research team shares responsibility, even though the PI directs the project and bears ultimate responsibility for its conduct.

The IRB must ensure that PIs have the training and experience that the project requires. Researchers are given considerable latitude, however, in designating the PI. The IRB is most likely to have concerns about projects in which the principal investigator appears to lack training and experience in human subjects research or has a conflict of interest that could make it difficult for him or her to ensure the subjects' well-being. If external funding is being sought, the University's policies on Principal Investigator Eligibility on Sponsored Projects also must be met. Some research projects include a proposal to delegate much of the recruitment or intervention to research associates. In those instances, an explanation of the training of the associates should accompany the application.

Whenever there is a change in the PI or in the PI's status that affects the project, the IRB must be notified. [See section 6.2 Making changes to research protocols]

3.10 Specifying the number of research subjects
The IRB is required to protect subjects from the first contact for possible recruitment. All subjects who go through the recruitment process even if they fail or decline participation screening must be accounted for. When asking for subjects please ask for a number large enough to account for this group.

The application must specify the number of study subjects to be recruited and tested, grouped by age, gender, and population diversity. Exceeding the recruitment limits approved by the IRB is a violation of the protocol. The IRB must give prior written approval for any increase in subjects.

If it is difficult to predict how many subjects will be eligible or be attracted to a study, the optimum number should be specified. Responses such as "don't know" or "as many as we can recruit" to questions about the number of subjects are not acceptable.

Multicenter studies, in which data will be pooled and recruitment may vary, present a special problem for investigators. The application should provide information about the total picture, including both the number of subjects to be studied at the University or by University researchers and information on overall recruitment goals.

3.11 Women and minorities in study populations

Research benefits and burdens should be distributed fairly. If an individual or group is denied access to a clinical trial that might be beneficial or if some people are singled out to bear the burden of risks associated with a study, the requirement for fairness is not met.

In accordance with the policies of the National Institutes of Health, the IRB requires researchers applying for federal funds to give breakdowns of their subject populations by gender and minority group. Studies with the potential to address issues relevant to both sexes must recruit both genders, and minority populations should be included in a study population wherever feasible. Researchers must justify the exclusion of any group of individuals. The IRB makes exceptions if there is adequate scientific justification for exclusion, such as when a disease predominates in one gender or the focus of the research question is on a specific group.

3.12 Students or employees as research subjects

Though the researcher may be careful to avoid potentially coercive behavior, the very nature of the relationship with the subject can create the appearance of coercion. For this reason, researchers should be aware of the potential for coercion that exists when a research subject is also a student, employee, colleague, or subordinate of the researcher. For this reason, researchers should avoid using their own students or employees as research subjects.

If there is a good scientific reason to include their own students, researchers should:

- Make sure students clearly understand that their participation will not influence class standing, grades, or other benefits under the control of the researcher.
- Limit the use of extra credit points as a reward for participating; points should be used only when the research is closely tied to the course subject matter and they should not raise a student's grade by a whole step (for example, from a B to an A).
- Avoid using class time to recruit subjects or complete study instruments.

Researchers who include colleagues or subordinates as research subjects, must be able to provide a rationale other than convenience for selecting them and must show that the recruitment method does not lead colleagues to think they will be compromised by not participating. Usually recruitment through bulletin board advertisements or by a third party is preferable.

Information about how students and colleagues will be recruited and how coercion will be avoided should be included in the information submitted to the IRB.

3.13 Children as subjects

All research conducted is subject to the application of 45 CFR Subpart D. In all cases, inclusion or exclusion of children is reviewed for appropriateness as defined in the regulation.
In general, if research involves greater than minimal risk, children can be included in the study population only if there is direct personal benefit to the child. This restriction applies to research in both the health sciences and the social sciences. A research protocol that involves anything more than minimal risk and that offers no potential benefit to the subject cannot involve children unless all conditions of 45 CFR 46.406 are met. Investigators claiming this provision in 45 CFR 46.406 should be prepared to provide rigorous justification.

3.14 Payments to subjects

Researchers may pay research subjects for their participation, but payment arrangements must be disclosed to and approved by the IRB and are subject to a stringent review. Subjects are not paid to assume risk, but can be compensated for the time and inconvenience involved in participating. Payment arrangements affect the fairness of recruitment plans, the balance of risks and benefits, and the adequacy of informed consent. Although there are no fixed formulas for determining whether payment plans are acceptable, the IRB restricts payment arrangements that appear to be coercive. Payment should not encourage subjects to participate or continue to participate against their better judgment.

The amount paid to subjects must correspond to the burdens of participation. For example, payment might defray parking charges or transportation costs. Payments may also be scaled to the time that subjects spend in a study or to the biological materials they donate. The minimum wage provides a ready baseline for hourly rates for participation, and the Blood Bank's payment scale for plasma and other blood products offers a guideline for compensating subjects for biological materials.

Researchers are encouraged to offer gift certificates/gift cards or grocery vouchers rather than cash or checks. When children and adolescents are the subjects, researchers are encouraged to reimburse parents for parking or transportation and give a token payment or gift certificate to the child subject. Drawings and raffles are subject to the state laws and regulations governing games of chance and are generally discouraged.

Subjects must receive at least partial payment if they withdraw from a study. Withholding all payment until participation is complete is coercive. A modest lump sum can be paid after the subject's participation is complete if the arrangement is thoroughly documented in the consent form. An end bonus cannot exceed half the total payment provided to subjects.

3.15 Advertising and recruitment

Advertisements are part of the informed consent process and subject selection process. Samples of all advertisements, such as flyers, newspaper ads, radio and television announcements, URLs, bulletin board tear-offs, and posters, along with an explanation of other methods of recruiting subjects, must be submitted to the IRB. Advertisements should be submitted with the application or as soon as the principal investigator decides to use them.

Advertisements should be limited to:

- names of the investigators and the university identified by name along with contact information,
- purpose of the research,
- general eligibility criteria, and
- straightforward and truthful descriptions of potential benefits, payment, or free treatment.

Advertisements should include the word "research" and should not claim, explicitly or implicitly, that the research is treatment or is superior to any current practice. Extravagant attention-getting devices such as extremely large, bold typefaces and dollar signs are prohibited. Statements of payment should not be in larger type than the rest of the ad. Advertisements should not pressure readers into participating.

The IRB's authority for review and approval of advertising is supported specifically by the FDA, 21 CFR 56.111(a) (3): PHS Information Sheet, January 1988.

3.16 FDA regulations for designating the principal investigator (PI)
Some additional requirements for PI designation apply to projects that fall under the guidelines of the Food and Drug Administration. The FDA defines an "investigator" as an individual under whose immediate direction a test drug or device is administered or dispensed to a subject. "Subinvestigators" are team members who may help design and conduct the investigation but are not charged with overseeing the investigation. Some team members such as pharmacists, research coordinators, and others who do not deal directly with subjects would not be listed as investigators.

Investigators involved in drug studies must sign an FDA State of Investigator agreement (Form FDA-1572), which documents the investigator's commitment to supervise the investigation. No standard agreement exists for device studies. Instead, the device study sponsor prepares a draft agreement and negotiates its terms with the investigator, following the FDA's regulations for investigational devices. Principal investigators should provide current copies of 1572 to the IRB.

The University IRB needs to be notified when a U of M faculty/staff member or student is identified on an FDA investigator agreement, so it can make sure that its records agree with the FDA's. The relevant federal regulations are 21 CFR 312 and 21 CFR 812, as well as the March 1995 FDA "Information Sheet."

### 3.17 Women in clinical trials

Food and Drug Administration guidelines implemented in 1993 give IRBs broad discretion to encourage the entry of women into the early phases of clinical trials. The guidelines now encourage women with childbearing potential to participate in entry phase 1 and early phase 2 trials. FDA believes that early drug trials can be safely conducted on women, even before all animal studies are completed, through sound protocol design. Studies can include pregnancy monitoring, pregnancy testing, and counseling about contraceptives or abstinence. Participants can also be referred to gynecologic consultants for advice. The guidelines also direct sponsors to collect gender-related data during research and development and to analyze the data for gender effects. New drug applications must include a characterization of drug effects by gender.

The guidelines stress that pharmacokinetic data on demographic differences should be collected beginning in phase 1 and 2 studies. When it is feasible, three pharmacokinetic issues should be considered when women subjects are involved:

1. the effect on the stages of the menstrual cycle,
2. the effect of exogenous hormonal therapy including oral contraceptives; and
3. the effect on the pharmacokinetics of oral contraceptives.

Consent forms should include a statement that there may be unknown risks to the fetus if a woman becomes pregnant while participating in a clinical trial.

### 3.18 Using investigational new drugs

Researchers who employ a test article classified by the Food and Drug Administration as an investigational new drug must assure the IRB that they are complying with the FDA's IND regulations (21 CFR 312). The IND number assigned to the test article must be filed with the IRB when the application for review is submitted.

Experimental drugs require an IND number if they are used to develop information about their safety or efficacy. Approved, marketed drugs may also require an IND, if proposed use is:

- different from its previously FDA-approved use,
- administered by an unapproved route or method of delivery, or
- an altered dosage form,
- shipped by interstate commerce in order to conduct a clinical trial.

The FDA has published several exemptions to the IND requirements. Roughly, a clinical investigation may be exempted from the IND requirements if the drug is lawfully marketed in the U.S. and all the following apply:
• the results will not be reported to the FDA to support a new indication for use nor to support any other significant change in the labeling of the drug;
• the investigation will not be used to support a significant change in the advertising of a prescription drug that is already on the market;
• the investigation does not involve a route of administration, dosage level, use in a patient population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
• the investigation is conducted in compliance with the requirements for institutional review set forth in Part 56 and with the requirements for informed consent set forth in Part 50; and
• the investigation is conducted in compliance with the requirements of section 312.7, which concerns the promotion and sale of investigational drugs.

The IRB requires detailed discussion of all these points when an exemption from IND requirements is requested.

3.19 Using investigational new devices

Researchers who employ a significant risk device classified by the Food and Drug Administration as an investigational device must assure the IRB that they are complying with the FDA's Investigational Device Exemptions (IDE) regulations (21 CFR 812 or 814). The IDE number assigned to the test article must be filed with the IRB when the application for review is submitted.

3.20 Labeling investigational drugs

Requirements for labeling investigational products are similar to those required for prescription medications. FDA regulations for labeling (21 CFR 3.12.6) indicate the following:

• The immediate package of an investigational new drug intended for human use shall bear a label with the statement "Caution: New Drug—Limited by Federal (or United States) law to investigational use."
• The label or labeling of an investigational new drug shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated.

In addition, state regulations for labeling prescription drugs apply to investigational drugs (see Minnesota Statutes 151.06 subd 1, 151.212 subd 1):

All drugs dispensed to or for a patient (other than an inpatient of a hospital) shall be labeled with the following:

1. Name, address and telephone number of clinic dispensing
2. Subject's name or identifying number
3. Prescription number, or way of tracking the dispensing
4. Name of prescribing physician
5. Directions for use
6. Name of manufacturer of the finished dosage form (there may be an exception due to investigational status)
7. Auxiliary labels as needed, e.g., "Take on empty stomach."
8. Date of original issue or renewal
9. Generic or trade name of drug and strength or study name to identify drug

There may be some flexibility allowed for labeling due to the unique nature of investigational studies, particularly studies involving a placebo.
### 3.21 Research involving ionizing radiation

To facilitate the review of applications for research involving radiation exposure, the IRB and the Human Use Subcommittee of the All University Radiation Protection Advisory Committee (HUS-AURPAC) have revised the applications to both committees.

Projects involving higher levels of radiation exposure, or exposure of vulnerable subjects (e.g. pregnant and/or breast feeding subjects, or minors), and/or subjects who receive a radiation dose above 100 millirem, require full review by the HUS-AURPAC. Projects that involve low-level radiation exposure (100 millirem or less) or routine clinical care and that have been approved by the IRB qualify for expedited review by the HUS-AURPAC chairperson.

**IMPORTANT:** if the radiation dose received by a subject in a study is a part of their normal medical care, and would be received even if they did not participate in the study, the study does not require review by the HUS-AURPAC.

Radiation exposures which may qualify for expedited review by the HUS-AURPAC chairperson are listed in Section 2. of the HUS application form entitled, Conditions for Accelerated HUS Review. The HUS application form is available on-line at [http://www.dehs.umn.edu/rpd/forms/HUS.pdf](http://www.dehs.umn.edu/rpd/forms/HUS.pdf) Listed below are some examples of ionizing radiation procedures for which accelerated review by the HUS may be authorized:

1. Single plane-film radiographic procedures that do not involve cineradiography, fluoroscopy, or any form of tomography, such as (a limited number of) X-rays of: joints; cervical spine; PA or lateral chest; PA, AP or lateral skull; AP scapula or shoulder; femur; AP, PA or lateral abdomen, AP pelvis; mammogram.
2. A limited number of nuclear medicine labeling procedures including Tc-99m and Xe-133.
4. Cancer therapy studies with a protocol that has already been reviewed by a national study group (for example, RTOG or CALGB), provided the study group's review criteria have been approved by the HUS-AURPAC.

Research conducted at another site requires review by the radiation review committee at that site. Our University IRB should receive documentation of that review.

Application sheets for HUS-AURPAC review are available on-line ([http://www.dehs.umn.edu/rpd/forms/HUS.pdf](http://www.dehs.umn.edu/rpd/forms/HUS.pdf)) or from the RSPP office and from the Radiation Protection Division (612/626-6764). If assistance is needed in completing dose calculations for HUS-AURPAC review, contact a medical physicist in the University's Department of Radiology (612-626-6805).

### 3.22 Emergency waivers

Physicians sometimes decide they must administer a drug, biologic, or experimental agent that has not yet been approved for marketing by the FDA. In such cases, the IRB can grant a waiver for an "emergency use." "Emergency use" is defined as the use of an experimental device on a human subject in a situation that is life-threatening, in which no standard acceptable treatment is available, and in which there is not enough time to obtain full IRB board approval.
When a physician must employ experimental medicines or devices to care for a patient in a life-threatening situation, neither the IRB nor the clock nor the calendar should interfere.

The IRB trusts physicians to exercise their best clinical judgment, to use experimental medications when necessary, and subsequently to take the appropriate steps to request approval or inform the IRB.

When emergency medical care must be provided without prior IRB review and approval, the patient may not be considered a research subject. The emergency care may not be claimed as research, nor may the outcome be included in any report of research activity.

**Procedures during business hours**

If the need for emergency use arises during the business day, the procedure to secure a waiver is as follows:

1. The physician notifies the IRB office by telephone of a pending request for emergency use.
2. The IRB administrative staff refers the physician to the IRB chair, or to a physician designated by the chair, to secure oral approval.
3. Within five working days of the request, the physician provides the IRB office with written documentation of the oral approval, a copy of the unsigned consent form used to document informed consent of the subject, and a report of the experience.
4. The IRB provides the physician with written confirmation of its approval. This should be maintained with the physician’s records.

Many drug companies require IRB certification of approval to release drugs or biologics. The investigator is responsible for the paperwork required by sponsors, drug companies, and the FDA.

**Procedures outside of business hours**

If the need for emergency use arises when the IRB office is not open, the physician should:

1. secure approval, or agreement, from another physician who is not involved in the treatment of this particular patient,
2. alert the IRB office of the intended use by voice mail at 612-626-5654 or email at irb@umn.edu, and
3. report the action to the IRB office in writing within five working days.
4. THE PROCESS OF CONSENT

Since the central requirement for human subjects research is that people participate voluntarily, the informed consent process is one of the most important parts of planning a research proposal. The process must assure that the potential subject understands the study and its risks and benefits and can certify his or her willingness to participate.

4.1 A process - not a form
4.2 When to discuss participation
4.3 What must be said about the research
4.4 What must be said about the conduct of the research
4.5 Assessing the subject's understanding
4.6 Documenting the subject's consent with a consent form
4.7 When to submit the form to the IRB
4.8 When the consent requirement can be waived
4.9 The Certificate of Confidentiality - an additional protection
4.10 Children and adolescents
4.11 Consent and language barriers
4.12 Cross Cultural Consent Issues
4.13 Research in acute care settings
4.1 A process - not a form

Since subjects retain the right to withdraw from a study, consent is an ongoing process. It starts well before any forms are signed and continues until the subject's participation is complete.

The informed consent process is different from the consent form. It involves meeting with a potential subject, finding out whether he or she is capable of giving consent, and discussing the purpose, risks, and benefits of participation. The consent form formalizes the agreement to participate and should be designed to document the process. Obtaining informed consent is not just giving a prospective subject a consent form and getting it signed.

If consent is to be informed, the subjects must genuinely understand the study. Hence, researchers should strive to convey information to subjects, not merely disclose it to them. Subjects should be able to demonstrate their understanding of the study procedures, risks, and benefits in which they are agreeing to participate.

4.2 When to discuss participation

To achieve understanding, potential subjects should not be presented information all at once or only at the last minute. People need time to think about whether or not they want to participate. They may wish to discuss the decision with family, close friends, or religious advisors. They should not feel rushed or coerced. They need time, especially if the information is disturbing or particularly complex, to digest the information and come to terms with it.

Information must be comprehensible. Even highly educated people need to have technical information presented in simple terms. How information is best expressed will vary with the population of course. In studies involving nurses as subjects, for example, researchers can explain a project using some medical terminology, but lay persons need to have information presented as simply and straightforwardly as possible. Some of the suggestions offered here for writing readable consent forms are also useful for presenting information in discussions.

4.3 What must be said about the research

Consent for research involving clinical procedures should be discussed during prior visits to the clinic, not on the day of the procedure. Whenever possible, subjects should be approached when they are rested, lucid, and able to use eyeglasses or hearing devices if they need them.

Federal regulations for human research identify some information as "essential" for understanding any research project [45 CFR 46.116(a)&(b)]. At a minimum, investigators should:

a. explain the purposes of the research;
b. report the expected duration of the subject's participation;
c. describe the procedures to be followed;
d. identify any procedures or products that are experimental;
e. explain why the subject is eligible to participate;
f. describe any foreseeable risks or discomforts that the subject will bear;
g. describe any benefits to the subject or to others that can reasonably be expected;
h. disclose appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
i. explain the confidentiality of any records that identify the subject;
j. explain, for research that involves physical contact or physical activity, whether compensation or medical treatment will be available if the subject is injured and where to get further information about this;
k. identify people who can answer questions about the research, including the principal investigator and a neutral third party who can explain the rights of research subjects and who should be contacted if the subject suffers injury related to the research. The "out-of-study" contact language for patients in the Fairview-University Hospitals and Clinics is as follows:
"If you have any questions or concerns regarding the study and would like to talk to someone other than the researcher(s), contact the Fairview Research Helpline at telephone number 612-672-7692 or toll free at 866-508-6961. You may also contact this office in writing or in person at Fairview University Medical Center - Riverside Campus, #815 Professional Building, 2450 Riverside Avenue, Minneapolis, MN 55454."
1. explain that participation is voluntary, that refusal to participate will involve no penalty or decrease in benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits.

In addition to this essential information, circumstances may require researchers to:

a. Explain that a treatment or procedure might involve currently unforeseeable risks (including risks to an embryo or fetus, if a participant is or becomes pregnant).

b. Explain conditions under which the investigator can remove people from the study without their concurrence.

c. Explain any additional costs that participating in the study might involve.

d. Discuss the consequences of and the procedures for withdrawing from the study.

e. Declare that research findings that could affect participants' willingness to remain in the study will be disclosed to them.

f. State the approximate number of people involved in the study.

g. Identify pilot or feasibility studies. Some subjects are willing to participate in a study that has a track record but are not willing to participate in a pilot phase. Participants need to be told if they are among the first people to receive the treatment or intervention.

h. Inform women of child-bearing age whenever a pregnancy test is part of the research protocol. They must also be told whether such tests will be repeated during the course of a research project and whether they must use contraceptives to participate in a clinical trial. Men, too, need to be told if contraception is recommended for them.

i. Make clear whether the procedures or drugs used in a study are standard, standard but used in a non-standard manner, or experimental.

j. If the study involves experimental drugs or devices, inform the subject that the research and medical records may be reviewed by the Food and Drug Administration (FDA) and by the company sponsoring the research.

k. Avoid stating that drugs or devices have been approved for human use by the FDA if any part of the study is outside the licensed and approved indications of those items. Patients interpret such a claim to mean that the FDA has licensed and approved this use of the item, not that the FDA has merely granted permission to investigate the use of the item.

l. Distinguish between consent to a study and consent to a treatment. In "treatment studies" (in which a patient who is undergoing a treatment is given a choice between undergoing it as part of a study or undergoing it in a standard health care context), the study and the treatment involve different benefits, risks, and alternatives.
   - If consent to the research and consent to the treatment can be confused, they should be presented in separate consent forms.
   - In discussing risks, the subject should be informed that there might not be any benefit to being treated "on study" instead of "off study."
   - In discussing risks, the subject should be informed whether the risks of being treated "on study" are different from the risks of being treated "off study."
   - In discussing alternatives, the subject should be told whether the study treatment (drug or device) is or is not available outside of the study context.

4.4 What must be said about the conduct of the research

Confidentiality

The researcher should describe the level of confidentiality of the research data and the measures that will be taken to ensure that confidentiality is maintained.

The phrase "only aggregate data will be presented" is appropriate only when it is true. Strictly understood, it means that the researcher will not describe a patient individually, even if the patient has a unique event. What is more common, however, and what the subject should be told, is that the subject's identity will not be disclosed.

Conflict of interest

The University Regents' Policy on Disclosure of Conflict of Interest (http://www1.umn.edu/regents/policies/academic/ConflictOfInterest.pdf) requires that researchers inform their
subjects of any conflicts of interest they have in the research. For example, researchers should disclose any stake they have in companies that might be affected by the research.

**Finder's fees**

Companies sometimes offer researchers incentives for recruiting subjects or conducting research on an investigational drug or device manufactured by the company. The incentive may be either a monetary fee or a donation of equipment or materials. Researchers should report these incentives to the IRB, which may require that this information be disclosed to prospective subjects.

**Payments to research subjects**

If researchers plan to compensate subjects for participating in a study, the consent form must describe the terms of payment and the conditions under which subjects would receive partial payment or no payment (for example, if they withdraw from the study before their participation is completed). See section 3.14 Payments to subjects

**4.5 Assessing the subject's understanding**

The responsibility of ensuring that someone who might participate genuinely understands the research and the risks and benefits involved falls upon the researcher, not upon the prospective subject. Hence it is critical to the consent process that the researcher not only field questions but also ask questions. Asking questions can further the discussion, elicit questions from the prospective subject, prompt the prospective subject to think more carefully about the project, and help the researcher decide whether the person has adequately understood the project. These questions must be prepared in advance.

Useful questions will be open-ended and non-directive. Rather than asking for yes or no answers, they ask for explanation because these questions often can be answered in a variety of ways, and do not already contain the correct answer. Open-ended questions are often introduced with "what," "where," "how often," "when," and "please describe." Examples of open-ended questions are:

- "Just so that I'm sure you understand what is expected of you here, would you please explain to me what you think we're going to ask you to do?"
- "Describe in your own words the purpose of the study."
- "What more would you like to know?"
- "What is the possible benefit to you of taking the new experimental drug? What are the possible risks?"

In contrast, examples of closed-ended and far less useful questions are:

- "Do you understand?"
- "Do you have any questions?"
- "Do you see that there are some risks to taking this drug?"

Instead of furthering the discussion, closed-ended questions tend to bring it to a stop and so should be avoided.

**4.6 Documenting the subject's consent with a consent form**

Once a subject understands a study and has expressed a willingness to participate, researchers must document the subject's consent with a consent form. Although a dated signature certifies the subject's willingness to participate, it is not equivalent to assuring that the subject has understood the research. Including a date with the signature avoids confusion about whether the subject began to participate before giving informed consent.

A researcher may need to prepare several consent forms, depending on who the subjects are likely to be. For example, a single project may require a consent form for the guardian or parent of a child, a consent form for the competent adult subject, and a simplified assent form for the 8- to 18-year-old or for the adult who is not competent to give consent alone. [See following sections for discussion of assent forms.] Foreign-language versions of consent forms will
be needed if people who do not speak English are to be enrolled. [See section 4.11 for discussion of translated consent forms. This section also discusses unexpected enrollment of non-English-speaking subjects.]

The person who prepares the documents should:

- Print all documents in type no smaller than 12 points to make sure they are readable. If the subjects will have difficulty with 12 point font, a larger font is necessary.
- Place the title of the study on the first page, exactly as it appears in the IRB files unless there is a compelling reason to shorten or change the title. "Informed Consent" is not an acceptable title because it obscures the fact that informed consent is a process, not the document itself, and implies a completeness that the form may not have.
- Number each page after the title page so that pages appear in a logical order and missing pages are readily noted (example: "page 2 of 4").
- Print the IRB code number assigned to the study on the consent form.
- Include a consent form version date. This date should be updated each time a new version of the consent form is approved by the IRB.

Format and specific requirements

The consent form should:

- **Identify the researchers by name along with their University and Departmental Affiliation on the first page of the consent form.**
  The form should not say that the study is "sponsored" or "endorsed" by the University.

  If the project is conducted by faculty or staff, the first page of the consent form should be printed on departmental letterhead. For student projects, the words "University of Minnesota" should appear in the header on the first page, and advisers' names and phone numbers should be given with the student's name and contact information.

- **Invite participation**
  Consent forms should "invite" participation. They should not say that a patient's physician or friend recommends participation, nor should they "offer the opportunity" to participate. It may be appropriate to point out that withdrawing from a study could have adverse consequences to subject treatment.

- **Summarize Cautiously**
  Information described earlier in the consent form should be summarized only in order to clarify. Summaries that suggest a warning or limitation of liability or opportunity for redress are not acceptable. Examples that are unacceptable are:
  - "You understand that..."
  - "The possible risks associated with this study have been presented."
  - "The method and purpose of administration of this study have been explained to you."
  - "You have been made aware of certain risks and consequences."

Readability and technical language

In writing consent forms, researchers should:

- Use declarative sentences suited for an eighth-grade reading level.
- Write in the second person ("you") rather than the first person ("I"), and avoid shifting from one to other.
- Avoid strike-out formats (such as "You/Your spouse/Your child"), since they depersonalize the form and often make it difficult to read.
- Keep the description of the study as brief as possible, even if the study is complex. The details can be placed in an appendix.
- List only the major risks associated with an experimental drug or procedure. Some effective consent forms simply state, "The risk of being on this study is that the treatment may not turn out to be as successful as we
hope, and may even be less effective than our previous standard treatment. In addition to this risk of being on the study, the drugs used in the treatment have their own risks and side effects. The most important ones are: "..." Again, the details go in an appendix.

- Use paragraph headings and illustrations. Use flow charts or calendar-like tables to explain studies that involve multiple visits, that ask subjects to go from one place to another, or that involve different protocols depending on research benchmarks.
- Describe quantities in lay terms (teaspoons, for example). Communicate size with an illustration or a reference to a common household object of the same size.
- Ask a neighbor, friend, or someone else who is unfamiliar with the field to read the final draft of a consent form. Software packages that evaluate a text's "readability" may be helpful.
- Replace technical language with lay terms. Some commonly used technical terms and possible replacements follow:

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute</td>
<td>new, recent, sudden</td>
</tr>
<tr>
<td>adverse effect</td>
<td>side effect</td>
</tr>
<tr>
<td>assay</td>
<td>lab test</td>
</tr>
<tr>
<td>benign</td>
<td>not malignant, usually without serious consequences</td>
</tr>
<tr>
<td>bolus</td>
<td>an amount given all at once</td>
</tr>
<tr>
<td>carcinogenic</td>
<td>capable of causing cancer</td>
</tr>
<tr>
<td>catheter</td>
<td>a tube for withdrawing or introducing fluids</td>
</tr>
<tr>
<td>chronic</td>
<td>continuing for a long time</td>
</tr>
<tr>
<td>clinical trial</td>
<td>an experiment with patients</td>
</tr>
<tr>
<td>controlled trial</td>
<td>a study in which the experimental procedures are compared to a standard (accepted) treatment or procedure</td>
</tr>
<tr>
<td>culture</td>
<td>test for infection, or organisms that could cause infection</td>
</tr>
<tr>
<td>double blind</td>
<td>study in which neither investigators nor subjects know which drug the subject is receiving</td>
</tr>
<tr>
<td>dysplasia</td>
<td>abnormal cells</td>
</tr>
<tr>
<td>edema</td>
<td>increased fluid</td>
</tr>
<tr>
<td>efficacy</td>
<td>effectiveness</td>
</tr>
<tr>
<td>extravasate</td>
<td>to leak outside of a blood vessel</td>
</tr>
<tr>
<td>hematoma</td>
<td>a bruise, a black and blue mark</td>
</tr>
<tr>
<td>heparin lock</td>
<td>needle placed in the arm with blood thinner to keep the blood from clotting</td>
</tr>
<tr>
<td>monitor</td>
<td>check on, keep track of, watch carefully</td>
</tr>
<tr>
<td>morbidity</td>
<td>undesired result or complication</td>
</tr>
<tr>
<td>mortality</td>
<td>death or death rate</td>
</tr>
<tr>
<td>necrosis</td>
<td>death of tissue</td>
</tr>
<tr>
<td>oncology</td>
<td>the study of tumors or cancer</td>
</tr>
<tr>
<td>percutaneous</td>
<td>through the skin</td>
</tr>
<tr>
<td>placebo</td>
<td>a substance of no medical value, an inactive substance</td>
</tr>
<tr>
<td>PRN</td>
<td>as needed</td>
</tr>
<tr>
<td>protocol</td>
<td>plan of study</td>
</tr>
<tr>
<td>random</td>
<td>by chance, like the flip of a coin</td>
</tr>
</tbody>
</table>
relapse the return of a disease
retrospective looking back over past experience

4.7 When to submit the form to the IRB

Researchers must submit consent forms when they first apply for IRB review and approval, and when they apply for continuing review. Since the standards for consent forms change over time, in part due to changes in regulatory mandates and community styles and expectations, the IRB reviews the form at renewal to ensure that it is up to date. In addition, the IRB may ask researchers to modify consent forms at other times, when circumstances warrant. Any revisions made to a previously approved consent form must be submitted to the IRB for approval before use.

4.8 When the consent requirement can be waived

On rare occasions, the federal regulations for human subjects research allow a waiver of the requirement for informed consent. For example, a waiver is possible if a study investigates certain aspects of public benefit or service programs (see 45 CFR 46.116[c]). Also, either a waiver or a consent process that omits or modifies the essential elements of informed consent is possible if the IRB finds that:

- the research involves no greater than minimal risk to the subjects;
- the waiver or alteration will not adversely affect the rights and welfare of the subjects;
- the research would be impracticable without the waiver or alteration; and
- the subjects will be informed of the study when it is over (if at all possible).

Only the IRB can waive or modify the consent process. Researchers are not authorized to make this decision.

4.9 The Certificate of Confidentiality - an additional protection

A "Certificate of Confidentiality" protects subjects' anonymity by protecting research records from subpoena. The assistant secretary for health in the Department of Health and Human Services issues the certificate under two conditions: the research is on a sensitive topic, and the protection is necessary to achieve the research objectives. The certificates are granted sparingly. The study's funding source is not relevant to the decision.

The certificate goes beyond the consent form in ensuring confidentiality and anonymity. Without the certificate, researchers can be required by a court-ordered subpoena to disclose research results (usually as part of a criminal investigation of the subjects).

Research can be considered "sensitive" if it involves the collection of:

- information about sexual attitudes, preferences, practices;
- information about the use of alcohol, drugs, or other addictive products;
- information about illegal conduct;
- information that could damage an individual's financial standing, employability, or reputation within the community;
- information in a subject's medical record that could lead to social stigmatization or discrimination; or
- information about a subject's psychological well-being or mental health.

This list is not exhaustive. Researchers contemplating research on a topic that might qualify as sensitive should contact the IRB office for help in applying for a certificate. The IRB sometimes requires investigators to apply for a certificate.

4.10 Children and adolescents

Written parental permission is required for studies involving children under the age of 18. If the research involves greater than minimal risk, signatures from both parents are required unless the second signature is not reasonably available. A single signature is sufficient if only one parent has legal responsibility for the care and custody of the child.
or if one parent is deceased, unknown, or incompetent. Parental permission is documented in a form similar to an adult subject consent form, tailored to invite "your child" to participate rather than "you".

On rare occasions, the IRB can grant a "waiver of parental consent," but only if the research will yield great benefit to the population being studied and if obtaining parental consent would pose a considerable risk to the potential subjects. Once parental permission has been obtained, the agreement of the child is required. Parental permission overrules a child's decision not to participate in therapeutic settings.

The child's agreement is documented with an "assent form," a child-friendly document that outlines the essential information about the research. All children 8 years through 17 years old should be given an opportunity to assent, since most children 8 years old have the cognitive and emotional maturity to understand a research project and to decide whether they want to participate in it.

Some children under the age of 8 may also be capable of granting and withholding assent, and the IRB asks researchers to be sensitive to the needs of these children on an individual basis. Researchers should try to draft a form that is age-appropriate and study-specific, taking into account the typical child's experience and level of understanding, and composing a document that treats the child respectfully and conveys the essential information about the study. The form should:

- tell why the study is being conducted;
- describe what will happen and for how long or how often;
- say it's up to the child to participate and that it's okay to say no or withdraw;
- explain if it will hurt and for how long and how often;
- say what the child's other choices are;
- describe any good things that might happen;
- say whether there is any compensation for participating; and
- ask for questions.

The document should be limited to one page if possible. Illustrations might be helpful, and larger type makes a form easier for young children to read. Studies involving older children or adolescents should include more information and may use more complex language.

In instances where critical therapeutic research is involved, parental permission overrules a child's decision to participate. In such cases, a child's dissent would not be honored; therefore an "information sheet" rather than an assent form should be used. The information sheet should include the same info found in an assent form except:

1. it should not indicate that the decision to participate is up to the child nor that it is okay to say no.
2. it should not include signatures.

Subpart D of 45 CFR 46.401-409, "Additional Protections for Children Involved as Subjects in Research," outlines the conditions of participation for minor subjects.

4.11 Consent and language barriers

When planning research which will include non-English speaking subjects, researchers should prepare both English-language and translated consent forms for proposals involving non-English-speaking subjects. An explanation of the translations and the expertise of the translator should be provided for IRB review. The IRB may consult with language experts or require a "back-translation" into English.

As an alternative to translated consent forms, an oral presentation of informed consent information in conjunction with a short form written consent document (stating that the elements of consent have been presented orally) and a written summary of what is presented orally can be approved by the IRB. A witness to the oral presentation is required, and the subject must be given copies of the short form document and the summary.

When this procedure is used with subjects who do not speak English:

- the oral presentation and the short form written document (see sample attached) should be in a language understandable to the subject;
• the IRB-approved English language informed consent document may serve as the summary; and
• the witness should be fluent in both English and the language of the subject.

At the time of consent, the following signatures should be obtained:

1. the short form document should be signed by the subject (or the subject's legally authorized representative);
2. the summary (i.e., the English language informed consent document) should be signed by the person obtaining consent as authorized under the protocol; and
3. the short form document and the summary should be signed by the witness. When the person obtaining consent is assisted by a translator, the translator may serve as the witness.

The IRB must receive all foreign language versions of the short form document as a condition of approval (see 46.117(b)(2)). Expedited review of these versions is acceptable if the protocol, the full English language informed consent document, and the English version of the short form document have already been approved by the convened IRB.

Download short forms (http://www.irb.umn.edu/consent/downloadshortforms.cfm) in different language (languages available: Arabic, Cambodian, Croatian, French, Hmong, Lao, Oromo, Russian, Somali, Spanish, Vietnamese)

Sometimes a subject understands English but does not read or write English. An impartial witness should document that the subject understands the study and the consent process and consented to participate.

4.12 Cross Cultural Consent Issues

The requirements for documenting informed consent vary among cultures. The IRB does not exempt projects conducted in foreign countries or with other cultural groups here from the consent requirement, but it can waive the requirement for written documentation of consent. In some settings, the process of signing the form is very intimidating and is thought to be riskier than the research itself.

Researchers planning to conduct cross cultural research should justify their proposed method of documenting consent. The justification should include a description of customs if they constrain the typical informed consent process. Subjects in foreign sites should be given local contacts for any questions they may have about the research or about their rights.

4.13 Research in acute care settings

Although the subject's consent must be obtained whenever possible, research on drugs or devices that are employed during emergencies is sometimes an exception.

Food and Drug Administration (FDA) regulations for human subjects research allow for an emergency exception to informed consent if the situation is life-threatening and if there is no alternative approved therapy with an equal or greater likelihood of saving the patient's life (21 CFR 50.23 [a]). The intent is to allow physicians, exercising their judgment about patients' conditions, to use innovative treatments on incompetent patients. (See 3.22 Emergency waivers)
5. SPONSORED PROJECTS: SPECIAL REQUIREMENTS

Most federal and private funding agencies will not award a grant for a research project involving human subjects until the Institutional Review Board has certified its approval. However, the University’s systems allow for concurrent processing of the human subjects review and the management review of a proposal.

5.1 The Proposal Routing Form
5.2 Special situations
5.3 Changing the title of a research project
5.4 Unfunded proposals
5.1 The Proposal Routing Form

The Proposal Routing Form (PRF) (submitted through EGMS) is the form the University uses to obtain and document required management approvals when seeking external funding. This form contains a number of assurances, one of which pertains to involving human subjects.

Ideally, all research proposals would be reviewed and approved to the IRB before the proposal is submitted for external funding. When this is the case, investigators should affirm the approval on the PRF by specifying the date that the IRB approval was given. (This is the date of the IRB meeting if the approval of the full committee was required, or the date cited in the letter confirming an expedited approval or an exemption. IT IS NOT THE DATE OF THE LETTER.)

Concurrent processing is more common. The proposal should be submitted to the IRB in time for a decision before the proposal due date or at the time of award consideration. The PRF, indicating that IRB review is pending and providing the date the project was submitted for review, may be started. When IRB approval is granted, the RSPP database is updated with the approval date at the time the investigator is notified. The Sponsored Projects Administration (SPA) will access this database and verify IRB approval prior to submitting the proposal to the funding sponsor.

5.2 Special situations

Submission to funding sponsor prior to IRB approval:
Occasionally, IRB approval may still be pending when SPA receives the proposal for submission. If the funding sponsor's policy allows submission before IRB approval, then SPA will submit the proposal. The investigator is then responsible for notifying the sponsor when IRB approval is received.

Funding awarded prior to IRB approval:
Although this is unusual, a funding sponsor occasionally will make a conditional award before IRB has granted approval of the research project. If this occurs, the funding sponsor will specify a time limit (usually sixty days or less) for IRB approval. Again, the investigator is responsible for notifying the sponsor when IRB approval is received.

"Development Proposals":
Proposals in the development or concept stage pose a dilemma for investigators, funding sponsors, and the IRB. Funding agencies may be unwilling to consider a proposal without IRB approval, yet given the early stage of the project, the investigator may not be able to provide a complete protocol or consent document. In these situations, the IRB may grant a “conditional approval” that will satisfy the sponsor, yet allow for additional review to protect the subjects. The investigator should include an explanation for the deficiencies in the application as well as a statement that research will not begin until the complete project has IRB approval.

Program project grants and training grants:
Program projects are large, multiproject studies designed to produce a coherent body of research from many subprojects. Training grants also may include a variety of subprojects. The initial application to the IRB should include the title of the overall program project, the principal investigator's name and contact information, and a list of the subprojects with the investigators' names and contact information for each. All subprojects in the program project must be submitted to the IRB separately. It is the responsibility of the principal investigator for the overall project to ensure that the subproject investigators submit their applications in time to allow for review and approval. The IRB will certify its approval of the overall project only after it approves all subprojects.

Additional endorsements:
Funding sponsors occasionally require additional documents or special assurances. If this situation arises, the investigator may contact the RSPP staff for additional signatures or forms.

5.3 Changing the title of a research project
Any change in the protocol of a research project must be approved by the IRB. Occasionally, however, an investigator wants to change only the title of a research project to make it more competitive for a particular funding sponsor.

**Changes in the title can be handled in two ways:**

1. If the original title will no longer be used, the principal investigator should explain the change in a letter to the IRB that includes the original title, the Human Subjects Code Number, and the latest IRB approval date. A revised consent form must be enclosed (since the consent form gives the project's title). If the change is approved, the most recent approval date for the original study will apply to the new title.

2. If the original title is to remain active but funding is sought from another agency for a different title, the investigator should write to the IRB office and request approval of an additional title. This request should certify that the study with the new title is identical to the study under the original title. The request should include a revised consent form as well as a copy of the grant application associated with the new title. This procedure may be used only when the research procedures are genuinely identical to those approved previously.

Several cautions apply to the second procedure:

- If the project does not receive funding and the investigator does not intend to use the title for another submission, the investigator should notify the IRB that the title will be "retired."
- The IRB does not want research titles to proliferate. Investigators who overuse the procedures may be prevented from employing them in the future.

Researchers must file for these changes at least 30 days before the grant submission date. In all cases investigators must provide a copy of the grant proposal.

**5.4 Unfunded proposals**

If a proposal is not funded, the investigator should inform the IRB whether or not the work will be conducted in the absence of external funding.
6. CONTINUING REVIEW

Institutional Review Board review is an ongoing process, not a one-time step. Regular reevaluation ensures that research is conducted responsibly. Even in responsibly conducted studies, a one-time review is inadequate, since risks can really be understood only after research has begun, and since the regulations for human subjects research are constantly being refined as the risks and benefits are better understood. Unexpected developments in a project can raise questions about the conduct of the research, and new findings can raise questions about the project.

6.1 Continuing review

- When continuing review is required
- What to report
- Level of review

6.2 Making changes in research protocols

- Absent & exiting principal investigators
- How changes are reviewed

6.3 New findings

- Adverse Events
- Events at other institutions in a multicenter trial
- Death of a research subject
- New risk/benefit findings

6.4 Keeping Records
6.1 Continuing review

"Continuing review" refers to regularly scheduled complete reappraisals of a project. The goals of continuing review are to ensure that the risk/benefit ratio is still acceptable, that the measures taken to safeguard subjects are adequate, that the approved protocol is followed, and that the project reflects any changes that have been made in the regulations for human subjects research since the last approval.

The IRB may require changes in protocol or revisions in the consent form if the study's risks were originally underestimated, but the converse can also occur: the investigators and the IRB may have underestimated the benefit to research subjects.

When continuing review is required

The Department of Health and Human Services (DHHS) Regulations 45 CFR 46, require that "an IRB shall conduct continuing review covered by this policy at intervals appropriate to the degree of risk, but not less than once per year..." This continuing review must be substantive and meaningful.

A notice for renewal and a "continuing review form" are sent to the principal investigator eight to ten weeks before the review date. The form should be completed and returned to the RSPP office by the indicated deadline. The study expiration date is crucial for the continuation of the study. If the study is allowed to expire, all data collection must cease and no funds may be spent. Any lapses in approval for the use of human subjects must be defended to the IRB and to regulatory or funding agencies. A new application and review will be required to reinstate the study if it expires. If the investigator does not respond to the final notice, the IRB will classify the study as "inactive."

The IRB is required to report all federally funded studies inactivated due to lack of response to requests for continuing review to the Office for Human Research Projects (OHRP). All IRB inactivated studies using investigational drugs or devices will also be reported to the Food and Drug Administration (FDA).

If the study is completed, an investigator is asked to complete several portions of the continuing review form as a "final report" on the project.

What to report

Continuing review requires that you complete the Continuing Review Form, attach a current consent form if subjects are currently being recruited and the requested summary letter. The Continuing Review Form requires the following information:

- the number of subjects enrolled since the last review and the total number of subjects enrolled to date;
- breakdowns of the subject population by gender and other demographics;
- a summary of the results of the research to date, including:
  - any unanticipated risks or adverse outcomes, and
  - any early indication that one of the treatments under study is significantly better or worse than others;
- any difficulties recruiting or retaining subjects, an explanation of the difficulties, and the number of subjects who withdrew from the study;
- changes in the last year that were approved and the dates they were approved;
- if currently recruiting subjects, a copy of the consent form currently in use (as most recently approved by the IRB); and
- documentation of FDA approval for investigational drugs, biologics, or devices used in the research that have received FDA approval since the last IRB review.
- change in relationship with the study sponsor might require conflict of interest disclosure under the Board of Regents' policy on Conflict of Interest

Incomplete forms will be returned, which may cause a delay in getting the study on the appropriate committee agenda.

Level of review
A project usually merits the same level of review in continuing review as it received originally. Hence, most projects require full review. As in the initial review, the IRB may require revisions in the protocol or the consent documents.

6.2 Making changes in research protocols

Once the IRB has approved a project, it must be carried out as planned. Any changes in subject population, recruitment plans, research procedures, study instruments, study sites, or major research personnel must be prospectively approved by the IRB. Enacted changes without prior approval constitute protocol violations.

Researchers planning a change should:

• write to the IRB office citing the title and code number of the approved study;
• describe the proposed change in lay language;
• explain why the change is needed (if the change is proposed by the sponsor or a national group, provide the sponsor's formal notice of a changed or revised protocol);
• describe the implications for the subjects; and
• provide revised consent documents, if the change will affect the human subjects.

Absent & exiting principal investigators

If a principal investigator is on sabbatical leave from the University, an interim PI must be appointed. The IRB should be informed of this person's qualifications and the new PI should write to the IRB accepting the responsibility for the treatment of subjects. If a researcher leaves the University permanently, the IRB should be notified both of any interim investigators and of the final replacement or the study will be filed as "inactive".

How changes are reviewed

Some minor changes are handled by administrative action. Many changes receive expedited IRB review. Changes that affect the risk/benefit ratio may require full review. Implementation of the change must wait for the IRB's approval.

6.3 New findings

Adverse Events

Adverse events are unexpected problems whose nature, severity, and frequency are not described in the information provided to the IRB or to participants. Examples include unexpected complications in a subject, missteps in the consent documentation, or breaches of confidentiality. Adverse events should be reported to the IRB within 10 working days. Sometimes a study must be suspended to ensure subjects' safety.

The report of the event should discuss:

• the facts of the case, including the date and a description of the subject;
• whether the event is related to the study's procedures or drugs or to the subject's underlying disease or condition;
• the steps that have been taken to address the problem;
• whether the event is likely to recur; and
• whether the event provides new information about the study's risks that should be conveyed to participants, in a revised consent form.

Reports of events occurring at other sites receive expedited review, but in some cases the full IRB is involved. All events that occur at the University of Minnesota are reviewed by a full IRB committee.

The University's policies on adverse events are based on Food and Drug Administration regulations. According to the FDA, a "serious adverse drug experience" with respect to human clinical experience includes "any experience that suggests a significant hazard, contraindication, side effect, or precaution," including "any experience that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or
overdose." An "unexpected adverse experience" is any adverse experience whose nature, severity, and frequency of risk are not described in the information provided for IRB review or in the consent form. (See 21 CFR 312.32)

**Events at other institutions in a multicenter trial**

If the project is a multicenter trial and the event occurred at another institution, the researcher must write a memo to the IRB describing the nature of the event, its severity, the likelihood that it will occur at the University, and the implications for future subjects.

**Death of a research subject**

Researchers should alert the IRB to the death of any study subject, whether the death is believed to be related to the study or not.

**New risk/benefit findings**

As a study progresses and the risks and benefits of participating in the study are better understood, researchers sometimes find that the study must be stopped. For example, in some placebo-controlled trials, preliminary findings may give compelling evidence that a new treatment is efficacious. It then becomes unethical to continue giving placebos. (This occurs most frequently in multicenter trials in which a central statistical center receives and processes large volumes of data from several sites.)

In such cases, the investigator should write to the IRB, describe the findings and the need to suspend the placebo portion of the study. If the IRB agrees, the researcher should identify all subjects who received a placebo and invite those subjects to continue in an "open label" study in which all subjects receive the study medication.

**6.4 Keeping Records**

Researchers should maintain a file of all documents concerning the use of human subjects in research, to include original paperwork whenever possible, and a copy of everything else. The principal investigator's records should be a mirror image of the IRB's records: where the IRB holds an original, the principal investigator should hold a copy, and vice versa.

The documents that researchers should have on file include:

- a copy of the original application submitted to the IRB, including the consent form and the research protocol;
- the original of the IRB's response;
- a copy of responses to IRB stipulations or requests for additional information;
- the original notice of final approval;
- a copy of the "Certification of Approval" sent by the IRB to any funding agencies;
- copies or originals of all other correspondence with the IRB;
- copies of completed "Continuing Review" forms and attachments;
- the original notice of renewal of approval and certification, where applicable; and
- copies of any inspection or audit reports.

Original signed consent forms should be kept in a secure location separate from correspondence with the IRB but readily available to inspectors. Whenever a subject is a patient of the Fairview Health System, a copy of the signed form should be placed in the patient's medical chart as a precautionary measure, in case complications with the research protocol occur and emergency medical treatment is required.

IRB records are subject to inspection by federal authorities. Sanctions for incomplete or nonexistent records include suspension of funding, fines, exclusion from future funding, and suspension of laboratory access.